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INVESTIGATION OF THE DISTENSION CAPACITY OF THE HUMAN GALLBLADDER

by

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The emptying capacity of the gallbladder during cholecystography has received much attention. The gallbladder is however not only capable of emptying, i.e. decreasing in volume, but may also distend, i.e. increase in volume.

TATERKA (1930) found that the gallbladder expanded during cholecystography after the intravenous injection of decholin, a bovine bile preparation with a choleretic effect. HULTÉN (1943) described a case in which ingestion of a fatty meal was followed not by a decrease but by an increase in the volume of the gallbladder. The capacity of the gallbladder to expand has not, however, been studied systematically during cholecystography. This paper is concerned with the capacity of the gallbladder to expand in health and in disease.

Material. The distension of the gallbladder was studied by cholecystography in 300 cases. Good concentration power and absence of stones were evident in 133 cases; of these subjects, 60 were volunteers who had never had abdominal pain and 73 had had pain suggestive of biliary disease.

Biliary disease was demonstrable at cholecystography in the remaining 167 cases. In 99 of these good filling of the gallbladder was obtained via the cystic

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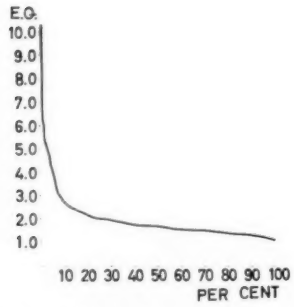


Fig. 1. Expansion quotient of the gallbladder. Distribution per cent in 300 cases according to degree of expansion. Average E. Q. 1.86.

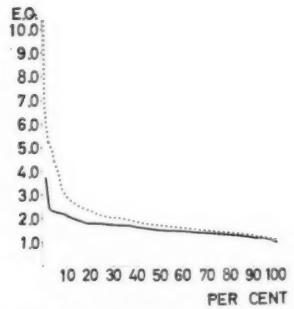


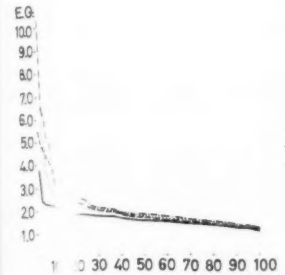
Fig. 2. Expansion quotient of concentrating (· · · · · · 232 cases, average E. Q. 2.01) and non-concentrating gallbladders (—— 68 cases, average E. Q. 1.60).

duct and the concentration power was normal; in 68 the concentration power was poor or absent. Thirty-two cases in which no filling of the gallbladder was obtained at the first examination were subsequently examined by intravenous cholegraphy.

Method. Cholecystography was carried out with the sodium salt of iopanoic acid (PETERHOF 1956). All examinations included films with the patient supine; in addition, in some cases in which the density of the contrast medium was high, frontal and lateral views were obtained with the patient erect. Repeated examinations of the same patient with the same contrast medium and with comparable projections showed that the size of the gallbladder is fairly constant.

Choleresis was induced in order to bring about an expansion of the gallbladder, and attempts were made to prevent the flow of bile through the papilla of Vater. Choleresis was produced by injection of Biligrafin-forte which, in the dog in a dose of 200 mg/kg bodyweight, will double the flow of bile for more than 2 hours (HORNYKIEWYTSCH 1956).

Biligrafin also produces choleresis in human beings. This effect was studied in association with postoperative cholangiography. The passage of bile to the intestine was retarded or inhibited by the injection of morphine (0.05 mg/kg bodyweight) in 14 subjects who had undergone cholecystectomy and had had a T-tube inserted. The flow of bile from the T-tube was measured at periods of 10 min before and after the intravenous injection of Biligrafin. The rate of flow was greatest 50 min after the injection and increased on the average by 70 % (from 3 to 5.2 ml), and always more than 40 %. REACH (1913) showed that morphine retarded or stopped the flow through the common bile duct. MCGOWAN, BUTSCH & WALTERS (1936) found that an injection of 1 mg of



		Average E. Q.
.....	60 patients with normal roentgen without symptoms	1.90
—·—·—	73 » » » » despite symptoms	2.10
— — —	99 » with concentrating gallbladder with stone	1.90
———	68 » » non-concentrating gallbladder	1.60

Fig. 3. Distribution per cent of expansion quotient in different groups.

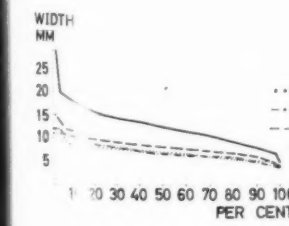
morphine raised the pressure in the biliary tract by 150 to 250 mm water in cholecystectomy cases with an indwelling T-tube. We obtained similar results in a preliminary investigation with selective measurements of the pressure following cholecystectomy without leakage of contrast medium along the T-tube at peroperative cholangiography.

The size of the gallbladder was measured during cholecystography; morphine (0.05 mg/kg bodyweight) was injected subcutaneously and at the same time 20 ml Biligrafin-forte were injected intravenously. Two hours later comparable views were obtained of the contrast-filled gallbladder.

Measurement of expansion of gallbladder. The contrast-filled gallbladder was measured planigraphically before and after the injection of Biligrafin and morphine. The ratio between the volume after expansion and before expansion, expansion quotient, E. Q., may be obtained from the following formula: The ratio of volumes =

$$\left(\sqrt{\frac{\text{Surface area during expansion}}{\text{Surface area during cholecystography}}}\right)^3$$

A gallbladder of high contrast density may appear larger than one of the same size but of lower density. In a given case, however, the contrast density is the same before as after expansion and the expansion quotient is given as a ratio.



		Average E. Q.	Average width mm
....	52 patients with normal roentgen without symptoms	1.97	6.7
-·-·-	58 » » » » despite »	2.10	6.9
- - -	89 » » concentrating gallbladder with stone	1.95	8.1
—	58 » » non-concentrating gallbladder	1.63	12.5

Fig. 4. Distribution per cent of width of common bile duct in different groups in a total of 257 cases, mean averages of E. Q. 1.91 and width 8.5 mm.

a b

Fig. 5. Normal cholecystography. a) Contrast medium in common bile duct. b) 2 hrs after injection of Biligrafin and morphine: distension of gallbladder.

Significance of projection. It was mentioned that in some cases (these totalled 51) of high contrast density, frontal and lateral views were obtained with the patient erect. It was generally found that the ratio of expansion did not vary with posture (Fig. 7). It is only in the supine posture that normally the gallbladder is filled completely with contrast medium, for bile containing contrast medium has a relatively high specific gravity, and the neck of the gallbladder and the cystic duct run dorsally to the common bile duct; furthermore, the heavier bile overflows into the common bile duct in this position (Fig. 5).

In 20 of the 51 cases it was possible to measure the width of the common bile duct with the patient supine and erect. This examination was performed to determine that the contrast medium was uniformly distributed and that no layer formation, which would affect the width of the common bile duct, had occurred when the patient was placed in the supine position. There was no evidence of any appreciable degree of layer formation between the bile mixed with contrast medium and the ordinary bile in the common bile duct (Fig. 10).

Expansion quotient of the gallbladder. The expansion quotient of the gallbladder varies widely (Fig. 1). In 80 cases (28 %) the volume of the gallbladder markedly increased after the injection of Biligrafin and morphine but in 60 cases

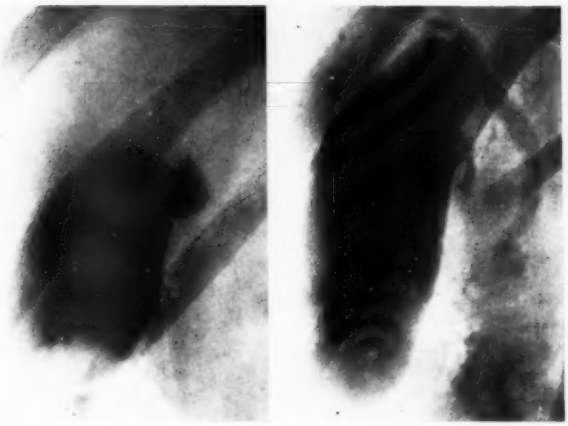


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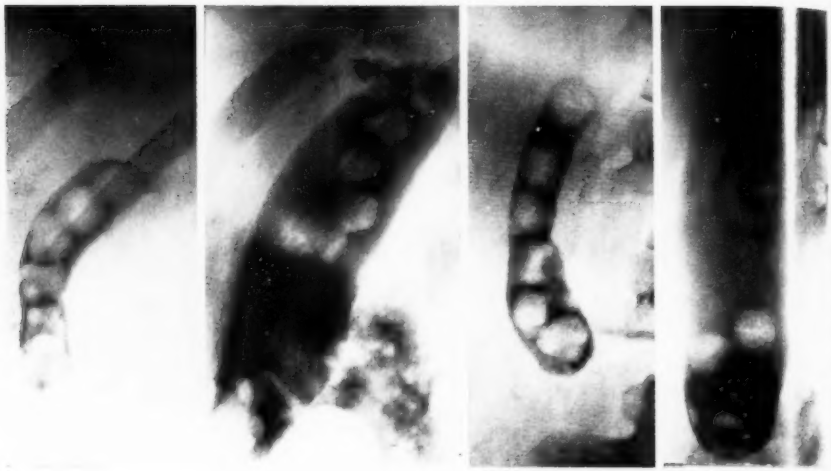
Fig. 6. Case with symptoms of biliary disease. a) Normal cholecystography. b) Considerable widening after injection of Biligrafin and morphine. Normal common bile duct.

(20 %) the expansion was only slight; the average for the entire material was 1.86 or about twofold.

The expansion quotient of filled and unfilled gallbladders is shown in Fig. 2. In the 232 cases in which the gallbladder was filled there was a twofold increase (E. Q. = 2.01) and in one third of the cases it was more marked (E. Q. = 3). In the 68 cases in which the gallbladder was not filled the average value was smaller (E. Q. = 1.6) and only in 9 cases (13 %) was there any considerable expansion (E. Q. = 2.40).

The expansion quotient in different groups is given in Fig. 3. The values in cases with normal findings at cholecystography (133) were the same as for the entire material with a gallbladder capable of concentrating contrast medium (232). Of these 133 cases, those with biliary symptoms (73) showed a higher degree of expansion (E. Q. = 2.10) than cases without symptoms (E. Q. = 1.90). In cases with stone but in which the gallbladder nevertheless filled (99) the degree of expansion was the same (1.90) as in normal cases without symptoms. Of the 68 cases in which the gallbladder did not fill the average expansion quotient was, as was mentioned, less and only in a few was it high.

Width of the common bile duct and the expansion quotient. Cases which have been subjected to cholecystectomy and which have postoperative symptoms often



a b c d

Fig. 7. Case with mild biliary symptoms. a) Supine. Stone in well filled gallbladder. b) Marked expansion quotient. c) and d) Erect. Expansion quotient unaltered.

show considerable widening of the biliary ducts after the injection of morphine during cholegraphy (GUNNARSON 1956).

In 257 of the present 300 cases it was possible to measure not only the expansion quotient of the gallbladder but also the width of the common bile duct and in some cases the widths of the hepatic duct and the right and left hepatic ducts were also determined. As to the width of the common bile duct (given in Fig. 4) an opposite tendency as compared with the gallbladder was noted; in the 58 cases of non-concentrating gallbladders, with a low expansion quotient (1.63), the common bile duct was usually wide (average 12.5 mm); in the 89 cases of stone in which the gallbladder filled and in which there was a high average degree of expansion (E. Q. = 1.95) the width was usually less (8.1 mm); in normal cases with and without biliary symptoms the width of the common bile duct was about the same (6.9 and 6.7). The mean for the entire material was 8.5.

Discussion

The gallbladder has two main normal functions, one being to concentrate and serve as a reservoir for the bile, which plays an important role in the metabolism of fat. Concentrated bile, in addition to its digestive action, also possesses a bacteriostatic quality. The reason why fair amounts of liver bile flow through the narrow and tortuous cystic duct instead of through the

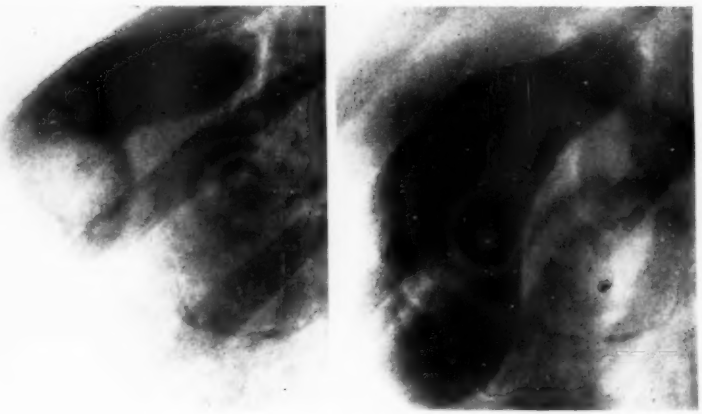


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Fig. 8. Case with chronic biliary symptoms. a) Cholecystography: good concentration of contrast medium, stone present. b) After Biligrafin and morphine marked expansion of gallbladder. Common bile duct of normal width.

wider common bile duct is because the latter can be shut off by the sphincter of Oddi. This occurs during fasting. The capacity of the gallbladder as a depot depends on the amount it can contain and its power of concentration.

The gallbladder also serves as a regulator of the intrabiliary pressure. This function was not realized until a few decades ago (POTTER & MANN 1926, IVY & SANDBLOM 1934, GERTZ 1946, EKDAHL 1953). It was the clinical observation that certain patients without mechanical causes such as stone or stricture of the common bile duct had biliary and intestinal symptoms after cholecystectomy that finally lead to the discovery of this function.

The concentrating power of the gallbladder has received much attention in considerations of biliary disease. It might be mentioned that GERTZ found postoperative symptoms after cholecystectomy in 27 % of patients in whom contrast filling of the gallbladder was obtained at preoperative cholecystography but in only 11 % of those in whom no such filling was obtained. The difference reported by EKDAHL was still more striking, 54 % and 7 %, respectively.

The importance of the gallbladder in a given case as a reservoir and as a pressure regulator depends on its capacity to concentrate and to expand. The latter quality may be deduced from the expansion quotient. The correlation between the concentrating power of the gallbladder and the expansion quotient is shown in Figs 2 and 3. It is clear from these figures that even in the presence of stones the gallbladder may still be able to expand if it can concentrate bile. Any decrease in the concentrating power is accompanied by a decrease in the expansion capacity, i.e. there is an approximate relationship between the con-

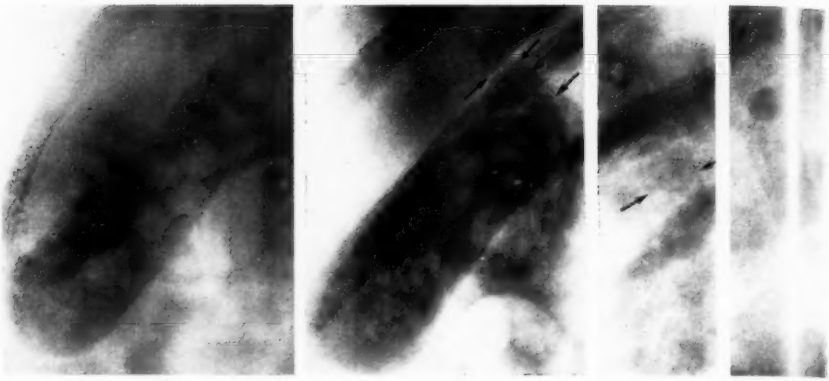

Fig. 9a Fig. 9b Fig. 10a Fig. 10b

Fig. 9. Case with chronic biliary symptoms. At cholecystography, no contrast medium in the gallbladder. a) 50 min after Biligrafin: moderate filling, stone present. b) 2 hrs after morphine: slight distension of gallbladder, width of common hepatic duct considerably increased.

Fig. 10. Case with chronic biliary symptoms. a) Intravenous cholegraphy with morphine, supine: moderate amount of contrast medium in common bile duct containing numerous stones. b) Erect: width of common bile duct unchanged but stones have now gravitated downwards.

centrating power and the expansion quotient. Observations made in the present investigation suggest, however, that in the evaluation of a given case the expansion capacity is to be preferred. Postoperative intestinal and biliary symptoms were found to be much more common after the removal of gallbladders which had filled at cholecystography than in those which had not filled. It is clear from Fig. 4 that the width of the common bile duct in cases in which the gallbladder did not fill and with a low expansion quotient was almost twice that found in cases in which the gallbladder showed concentrating power and marked expansion. This suggests that the volume of the bile ducts increases and thereby, at least partly, compensates for the loss of function of the gallbladder as a reservoir and pressure regulator.

SUMMARY

The expansion quotient of the gallbladder was studied during cholecystography with choleresis by the injection of Biligrafin and closure of the spincter of Oddi by the injection of morphine. The relationship between the concentrating power of the gallbladder and the expansion quotient as well as the width of the common bile duct was studied. The results are discussed in relation to so-called postoperative dyskinesia.

ZUSAMMENFASSUNG

Es wurde der Expansionsquotient der Gallenblase während Cholecystographie und Choleresе mittels Injektion von Biligrafin, und die Schliessung des Sphincter Oddi mittels Morphin-

injek n studiert. Es wurden auch die Beziehungen zwischen dem Konzentrationsvermögen der G lenblase und dem Expansionsquotienten wie auch die Weite des gemeinsamen Gallengang ntersucht. Die Resultate werden in Bezug auf die sogenannte postoperative Dyskinesie bespr hen.

RÉSUMÉ

L'a eur a étudié le quotient d'expansion de la vésicule biliaire au cours de la cholécystograph avec cholérèse par injection de Biligrafin et fermeture du sphincter d'Oddi sous l'effet une injection de morphine. Il a étudié les relations entre le pouvoir de concentration de la sicule biliaire et le quotient d'expansion, et le calibre de la voie biliaire principale. Il exa ine ces résultats en les rapprochant de ce qu'on appelle dyskinésie post-opératoire.

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ALUMINIUM PNEUMOCONIOSIS

A roentgendiagnostic study of five cases

by

NILS P. G. EDLING

The effect on the lungs of aluminium inhaled as a fine powder in large quantities has been a subject of conflicting opinions. No clinical or radiologic evidence has been produced in examinations of aluminium workers in Great Britain and the United States, whereas German investigators during World War II reported on a number of aluminium workers displaying roentgen changes indicating pulmonary fibrosis. During the stamping of powdered aluminium in the United States the powder is coated with a thin film of stearine: this gives rise only to foreign body reactions and does not cause pulmonary fibrosis. Stearine was unobtainable in Germany during the war and a paraffin substance was used in its place. The paraffin and not the aluminium has been held responsible for the lung fibrosis (SHANKS and KERLEY 1950). It is probable, instead, that the paraffin layer might have been defective and not capable of protecting the alveolar tissue from the particles of metal.

CAMPBELL et coll. (1957), in a review of observations and reports of many investigators on the effects of aluminium on human subjects, stated that the inhalation of aluminium or its oxide or hydrate, does not injure the pulmonary system. According to this view, no true aluminosis of the lungs should

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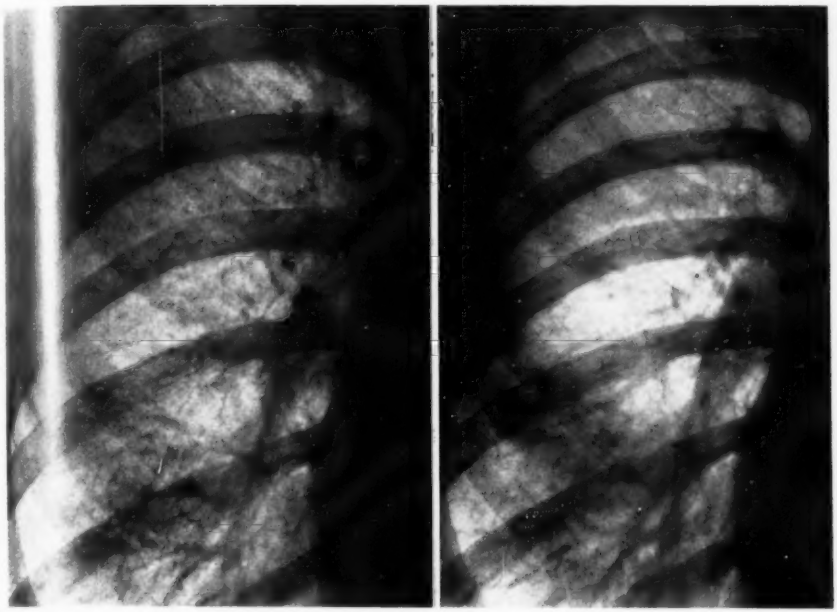

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Fig. 1. Case 1. Aluminium pneumoconiosis. a) 1950. Extensive fine linear pattern and small nodules with small patchy densities in upper lobe. b) 1953. Only a fine linear pattern persists. No pulmonary contracture.

exist. Other studies, however (GORALEWSKI 1950, SCHINZ-BAENSCH-FRIEDL-UEHLINGER 1952, LEDERER 1953, FORSSMAN et coll. 1961), seem to have established that the inhalation of aluminium dust may produce fibrosis.

Roentgenologic features observed in five patients long exposed to air containing aluminium dust form the subject of this paper; these five cases are the only ones with lung changes in aluminium workers reported in Sweden. All the clinical indications of aluminium dust pneumoconiosis were present (FORSSMAN et coll. 1961).

Material. The 5 patients belonged to a group of about 35 factory operatives who, during a certain period of their lives, were engaged without protection in stamping of powdered aluminium. The aluminium scrap used was of a high degree of purity, and the air contained a very considerable amount of dust. These operatives at the end of a working day looked like metal statues.

Random tests made with filter papers and impingers showed that the aver-

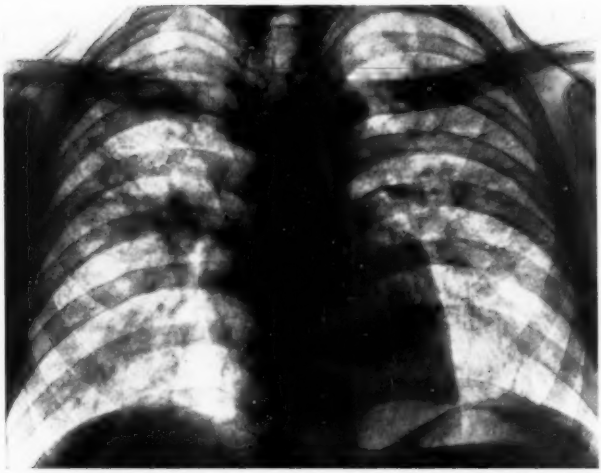

Fig. 2. Case 2. Aluminium pneumoconiosis. 1950. Extensive linear pattern and small nodules with a few areas of hazy opacity, mainly in the apical and middle zones. Hila and trachea slightly displaced.

age dust content varied between 4 to 50 mg/m³, and was sometimes much higher; most of the particles were smaller than 4 μ (FORSSMAN et coll. 1961).

After four of the patients had been exposed to the aluminium dust for periods ranging from 2 to 4 years, and the remaining one for 13 years, they developed symptoms mainly in the form of breathlessness. The workers either left the factory or were given work that did not involve the inhalation of dust. After some time three of them were entirely free from dyspnoea and regained full working capacity; the condition of the remaining two deteriorated and resulted in total disablement; one died. In the latter case post-mortem examination revealed non-specific inflammatory changes of a chronic character, with fibrosis and emphysema of the lungs.

None of the patients had been exposed to dust containing free silica. One of the patients was thought to have tuberculosis when he first developed chest symptoms, a diagnosis which was not confirmed by careful observation over a period of some months.

Case reports

Case 1. Male, aged 60. According to reports, a roentgen examination of the lungs in 1946 had shown no abnormalities. In 1950, extensive fine striations and minute nodular opacities were observed in both lungs and patchy densities in the upper lobes (Fig. 1a). No hilar or pleural changes. Repeat lung examinations from 1950 to 1960 showed that the changes had diminished (Fig. 1b), and that only a moderate amount of fine striations persisted. There was no evidence of pulmonary contracture.

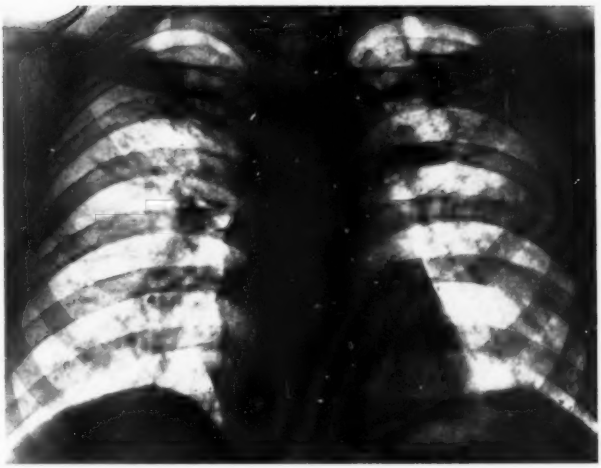

Fig. 3. Case 2 (same as in fig. 2). 1953. Coarse linear pattern and patchy areas of opacity in apical zones. Basal emphysema. Increased pulmonary contracture. Small pleural adhesions.

Case 2. Male, aged 35. Roentgen examinations of the lungs carried out in 1949 had shown extensive small nodular opacities in the apical zones of both lungs and patchy densities in the apical zone of the right lung. Roentgen examination a year later (Fig. 2) revealed that the middle zones and to some extent the lower zones had become involved. The hila were displaced slightly upwards and backwards and the trachea to the right, indicating some degree of pulmonary contracture. Small pleural adhesions to the diaphragm were present. An examination performed in 1953 (Fig. 3) showed that the nodules had almost disappeared but there were coarse striations and patchy densities in the upper zones; the contracture had increased. There was evidence of emphysema at the bases. The contracture and emphysema increased only slightly from 1953 to 1960.

Case 3. Male, aged 45. Roentgen examination of the lungs in 1947 had shown small nodules in the lungs, which at an examination in 1948 had progressed to wide striations with contracture of the lungs. An examination two years later revealed extensive striation and moderate contracture, mainly posteriorly in the upper zones, with displacement of the hila upwards and the trachea to the right. Emphysema and some opacities were present in the basal zones, and small pleural adhesions at the left diaphragm. Repeat examinations during the next ten years showed slightly increased contracture of the lungs.

Case 4. Male, aged 48. Roentgen examinations of the lungs, carried out in 1946, had shown extensive striations and patchy rounded opacities, some of a miliary type, and emphysema; a year later the rounded opacities were no longer visible. A roentgen examination three years after that (Fig. 4), revealed extensive patchy rounded densities and striations in the upper and middle zones, with displacement of the hila upwards and backwards, and of the trachea to the right. The lower zones were slightly affected. Basal emphysema was present, and the pleura was thickened at the mediastinum and diaphragm. The findings were unchanged during the next three years.

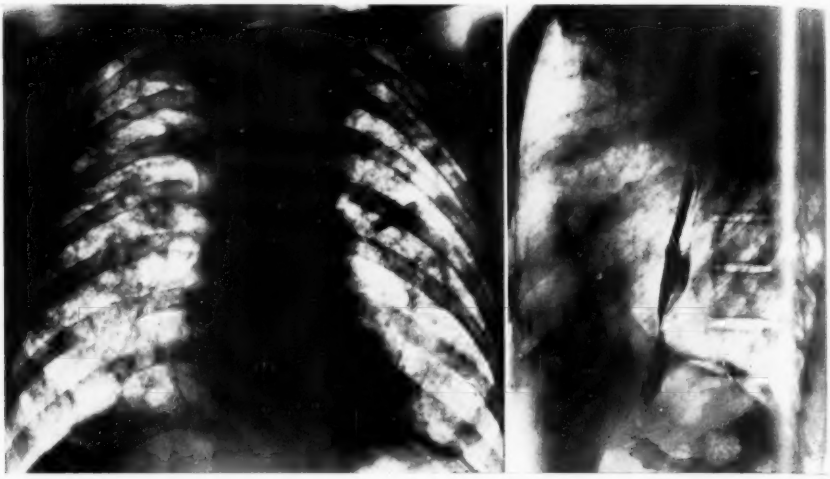

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Fig. 4. Case 4. Aluminium pneumoconiosis. Extensive linear pattern in apical and middle zones, with some involvement of basal zones; evidence of emphysema in latter regions. Displacement of hila. Pleural adhesions. Diaphragm flattened.

Case 5. Male, aged 64. According to reports, a few calcifications were visible in the lungs in 1946 but there were no other changes. Roentgen examination in the following year (Fig. 5) revealed fine and coarse striations mainly posteriorly in the upper zones, with incipient pulmonary contracture. The diaphragm was flattened; on the left side the pleura was thickened. Three years later (Fig. 6) the opacities in the upper zones and the contracture had increased, with displacement of the hila. There were some striations in the basal zones and evidence of marked emphysema. At repeat lung examinations from then to 1960 the parenchymal changes, the contracture and the emphysema had further increased. The trachea was displaced and there were now extensive pleural adhesions (Fig. 7).

Comments. All five cases presented evidence of fine striations or nodular rounded opacities. In four of the cases coarse striations and pulmonary contracture, as well as basal emphysema and thickening of the pleura had developed in from 1 to 2 years. Further follow-up examinations showed that in three cases the lung either remained unaltered or increased slightly and, in one case, markedly progressed. The observation time was 3 years in one case, and 10 years in each of the remaining three cases. In the fifth case the initial changes diminished and no pulmonary contracture occurred during an observation period of ten years. It is noteworthy that this case had had the longest time of exposure to the irritant.

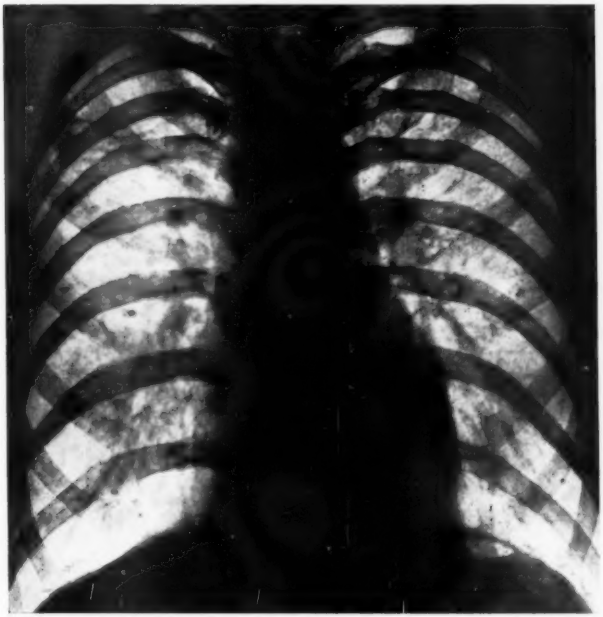


Fig. 5. Case 5. Aluminium pneumoconiosis. 1947. Fine and coarse linear pattern in upper zones; basal emphysema. Slight displacement of hila. Diaphragm flattened.

Discussion

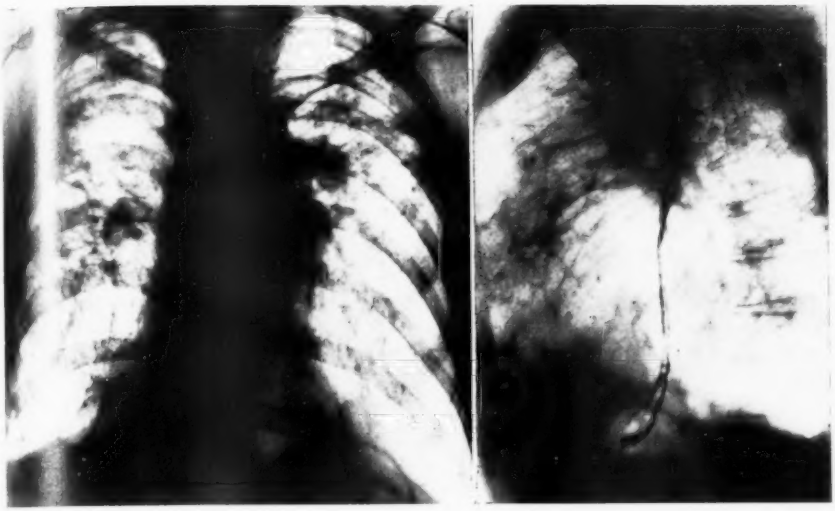
Despite the doubts expressed regarding the existence of aluminium pneumoconiosis, there seems to be no doubt of the clinical nature of the five cases under review. These patients were the only ones affected out of a group consisting of some 35 operatives engaged in the same work; this points to an individual disposition factor. There was no case of pneumoconiosis in a parallel group of workers in the same factory which were occupied in manufacturing 'gold-bronze' and exposed to air that was just as dustladen.

A striking feature in the roentgenologic follow-up examinations of the lungs in four of the cases was the rapid development from initially fine striations or nodular densities to fibrosis with pulmonary contracture and thickening of the pleura. This transition took place within a period of one or two years. After the fibrosis had occurred, further observations during a period of 10 years in three cases, and of three years in one case, revealed, with one exception, no or only very slight progress. In this latter case the changes developed into coarse striations and massive opacities which to some extent resembled the appearances in stage III of silicosis; the pleural involvement also increased.

Fig. 6. Case 5 (same case as in fig. 5). 1950. Increase of the emphysema and contracture.

In the fifth case the initial changes decreased and gave way to a moderate distribution of striations; no pulmonary contracture or emphysema was evident. The findings in all the cases agree well with those summarized by WORTH and SCHILLER (1954) from the relevant literature; these authors maintain that the phenomena cannot be adequately separated into different stages as in silicosis.

The roentgen findings in the five cases under review indicate in general a less fibroblastic activity in the lungs than that found in silicosis. This did not seem to depend on less exposure to the irritant, as the quantity of aluminium dust was relatively great and the exposure time was long. It was not possible to demonstrate the development of the initial changes into large nodules in any of the four progressive cases. Moreover, even if fibrosis developed to a considerable extent, it was found subsequently to progress only in one case during the many years that the patients were kept under observation. However, despite the standstill during three years one of the patients died. It is also noteworthy that in the different cases the roentgenologic aspects of the pulmonary contracture and emphysema were similar, which indicates resemblance with observations made in cases of silicosis, in which the pulmonary



a b

Fig. 7. Case 5 (same case as in figs 5 and 6). 1960. Areas of massive opacity laterally in upper zones; advanced emphysema of basal zones. Pleural adhesions. Marked pulmonary contracture with trachea displaced to the right.

changes in workers subjected to the same type of exposure are characteristic (BRUCE & JÖNSSON 1943). In silicosis, however, there are greater variations in the densities from one case to another as well as in the progress of the disease. The pleural involvement in two of the cases was fairly advanced.

Despite the persistent fibrotic changes, two of the patients had no symptoms after the initial dyspnoea and were passed for insurance as fit for work. In one of the cases the disease exhibited a regressive course with initial changes that diminished; this never occurs in silicosis. The working capacity of the patient was also unimpaired.

The relatively mild course of the disease may be explained by the fact that aluminium particles when inhaled display a mechanism different from that of silica particles and exert a less stimulating effect upon the formation of fibrous tissue; moreover, they are resorbed and transported from the lungs fairly quickly. This is supported by the postmortem examination of one of the cases in which only fibrosis and no aluminium was found.

The features described are not sufficiently characteristic to be classed as diagnostic. As in other types of pneumoconiosis, the diagnosis is always difficult and must be based on the history together with roentgen findings reviewed in juxtaposition.

SUMMARY

The roentgen appearances of the lungs in five workers exposed to aluminium d[ust] are described and discussed. Initial fine striations and nodular opacities, followed by fibro[sis] with pulmonary contracture and emphysema, and pleural changes, were demonstrate[d]. The fibroblastic effect of aluminium on the lungs seems to be less active and more tran[sient] as compared to that of silica.

ZUSAMMENFASSUNG

Das röntgenologische Aussehen der Lungen von 5 Arbeitern, die Aluminiumsta[ub] eingeatmet hatten, wird beschrieben und diskutiert. Initiale feine Streifigkeit und [knotiö]se Verdichtungen, denen eine Fibrose mit Lungenschrumpfung, Emphysem und pl[eu]ralen Veränderungen folgte, werden demonstriert. Die fibroblastische Wirkung des Alum[inium]s auf die Lungen scheint weniger aktiv und vorübergehender zu sein als die des Quarz[es].

RÉSUMÉ

L'auteur décrit l'aspect radiologique des poumons de cinq ouvriers exposés à la p[oussière] d'aluminium. Il a constaté au début de fines striations et des opacités nodulaires, suivies par une fibrose et une rétraction pulmonaire avec emphysème et lésions pleurales. L'effet fibroblastique de l'aluminium sur les poumons semble moins actif et plus transitoire que celui de la silice.

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FRO HUC THE EDWARD MALLINCKRODT INSTITUTE OF RADIOLOGY (DIRECTOR: PROF. M. WILSON), WASHINGTON UNIVERSITY SCHOOL OF MEDICINE, ST. LOUIS, MISSOURI, U. S. A.

ANGIOGRAPHY OF MALIGNANT TUMORS IN MICE

by

ALEXANDER R. MARGULIS, ERIK CARLSSON and WILLIAM H. MCALISTER

Angiography is used extensively in the study and diagnosis of neoplasms (2, 3, 4, 5, 6, 7, 10, 11, 12, 13, 14, 15). The correlation of the angiographic appearances with the histology of neoplasms has met with varied success. WICKBOM was able to differentiate certain brain tumors by vascular studies (16), Dos SANTOS claimed that a characteristic arrangement of vessels constituted evidence of giant cell tumors of bone (5), and LINDGREN suggested that all tumors have more or less specific angiographic appearances (9). A typical arrangement of blood vessels for each neoplasm or groups of neoplasms is difficult to determine from available reports because of the small volume of the case material and lack of identical methods of study. Even careful reports like those of LAGERGREN, LINDBOM and SÖDERBERG (8) or BORELL, FERNSTRÖM and WESTMAN (13) are based on only a few cases.

Large numbers of tumors in various stages of growth are needed to establish whether characteristic appearances exist, and if preliminary conclusions are to be reached within reasonable time experimental animals must be used. Final conclusions will be reached in human material.

Preliminary studies suggest that the degree of malignancy of neoplasms bears a relationship to the vascular configuration (Dos SANTOS, LINDGREN, LAGERGREN inter al.) (5, 9, 8). Greater knowledge of the significance of the

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appearances from the viewpoint of the history of the tumors may add t the understanding of the behaviour of the latter. The practical advantages f an indication of the histology of tumors prior to operation are self-evident. This preliminary report is based on a series of experiments in which angiog phy was performed in a large number of mice with transplanted and spontan usly malignant tumors. The vascular systems were injected in an identical m ner and the angiograms were enlarged and studied for similarities and differ ces. The experiments were designed to determine whether: (1) Specific reprod ible vascular configurations exist for different neoplasms, (2) the angiogr phic appearances depend on the host, (3) a given tumor has a similar vascu rity in different strains of mice, (4) if different types of neoplasms produce ch rac-teristic but different appearances in the same strain of mice, (5) if the vascu rity remains the same while the tumor grows, and finally, (6) if spontaneous t nors have the same vascular appearances as their transplants.

Material. The investigation was based on the angiograms of 171 tumor-bearing adult mice. Angiograms of 40 additional mice were excluded either because the tumors were too small, or because the angiographies were technical failures. Normal mouse angiograms, performed to develop the technique of examination, were also excluded. The types of tumors examined and the strains of mice in which they grew are summarized below:

Type of tumor	Host	Number of studies
Transplanted squamous cell carcinoma	Swiss 51	13
Spontaneous carcinoma of breast	C3H and Swiss 51	14
Transplanted carcinoma of breast	C3H and Swiss 51	46
Hepatoma	C57 L	24
Lymphosarcoma	C3H	29
Sarcoma — 37	DBA/1	17
Rhabdomyosarcoma	C3H	28
		Total 171

Method. The tumors were transplanted into the subcutaneous tissues of the flanks of adult mice; in a few cases the transplant was made into the muscles of the thigh. Micropaque (Colloidal barium sulphate) was used because it is frequently arrested in the arterioles and usually does not pass through the capillaries; it was hoped that this would afford a means of studying only the the arterial phase of tumor vascularity.

The angiograms were performed with a PE 160 polythene catheter placed in the exposed left ventricle after the mice were anesthetized. In the majority of cases films were obtained after the injection of 1, 2, and 4 ml Thorotrast (Testogen & Co). In thirty-four mice a fine suspension of Micropaque (Nancy & Co Ltd) was injected and a single exposure made. The injections were

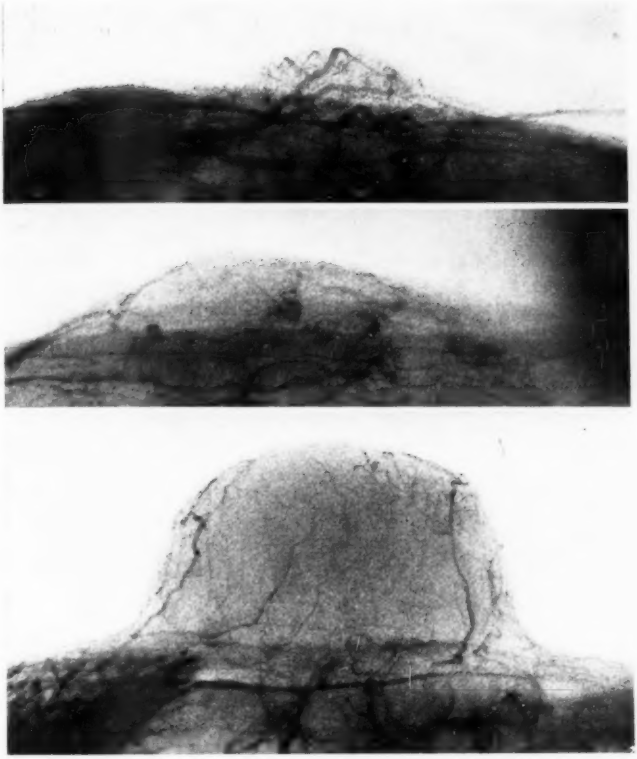

Fig. 1. Illustrative examples from a growth study of transplanted squamous cell carcinoma. Scarcity of vessels. The resistant pattern is apparent.

made manually with gentle pressure. Eastman Kodak Industrial Type M film and a 0.3 mm roentgen tube were used. The angiogram of the tumor and surrounding structures were enlarged ten times (linear magnification) and the photographs studied by three independent observers. Tumors of the same histologic type were first examined together and various groups then compared for similarities and differences in vascular appearances.

Squamous cell carcinoma

Swiss 51 mice (obtained from Dr. Suntzeff of the Cancer Research division) were studied: 10 with Thorotrast and 5 with Micropaque injections. The choice of the contrast media did not influence the angiographic appearances

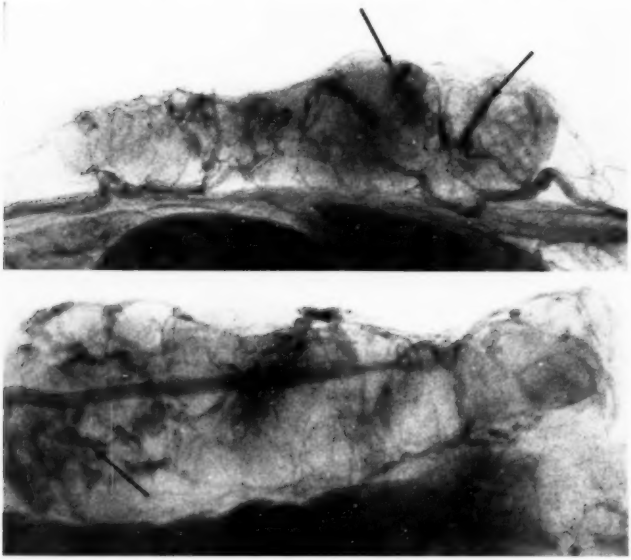

Fig. 2. Two examples of transplanted hepatomas. The vessels show a tendency to encircle lobules. Prominent saccular formations filled with contrast medium (arrows).

which were similar in all the tumors. There was a tendency for the neoplasm to assume a rounded shape and, when large, to become cystic. Large vessels encircled the tumors to form a coarse network, the tumors themselves being poorly vascularized. The blood vessels immediately below the tumour tended to run parallel to the body surface (Fig. 1). With the injections of Micropaque, arteries and veins in the tumors were demonstrated, which suggested the presence of vessels larger than capillaries, and appeared to act as arteriovenous communications.

Hepatomas

C 57 L mice with tumors (obtained from the Jackson Memorial Laboratory) were studied: 19 with Thorotrast and 5 with Micropaque. The Micropaque injections on the arterial side of the circulation filled veins and did not differ from the angiograms obtained with Thorotrast. Large superficial vessels were present. Grossly the tumors had a spherical shape and were raised from the body surface. In 14 of the 19 mice injected with Thorotrast, and in 3 of the 5 injected with Micropaque, the vessels showed a tendency to encircle portions of the tumor and form lobules (Fig. 2). Thirteen of the 19 tumors injected with

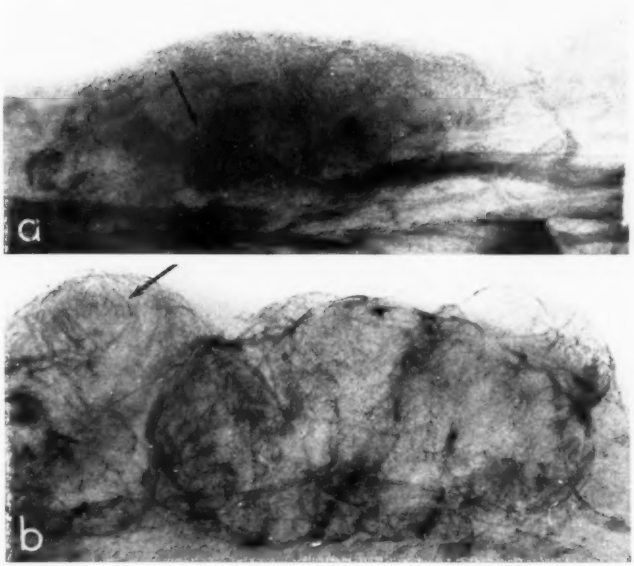

Fig. 3. Transplanted breast tumors in mice (a) injected with Thorotrast and (b) with Micropaque. The vessels have a tendency to encircle lobules. Parallel small vessels ('brushes') are seen (arrows).

Thorotrast and all of the tumors injected with Micropaque had small saccular structures filled with contrast medium. In 16 of the 24 hepatomas these sacs were arranged in clusters (Fig. 2).

Transplanted adenocarcinomas of the breast

Thirty-three adenocarcinomas of the breast in C3H mice (approximately evenly distributed between C3HBA and H2712J from Jackson Memorial Laboratory) and 4 transplanted breast tumors in Swiss 51 mice (from our Cancer Research Division) were injected with Thorotrast.

Of the 9 transplanted breast tumors injected with Micropaque, 8 were in C3H mice and 1 was in a Swiss 51 mouse. No significant difference was apparent between the appearances of the vessels in tumors injected with Thorotrast and Micropaque or in the two strains of mice studied Grossly there was a tendency for the tumor to be lobulated. The vessels on the surface of the tumor were generally not very large. The tumors were somewhat less vascular than hepatomas but more vascular than squamous cell carcinomas. The vessels tended to form lobules (Fig. 3). In 35 of the 46 tumors (76 %) small vessels of

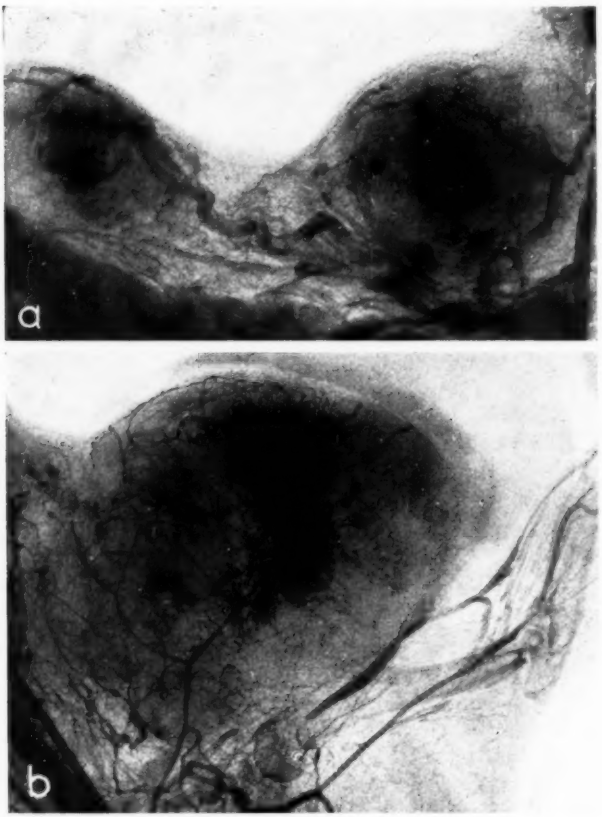

Fig. 4. Two examples of spontaneous breast tumors (a) in a C3H mouse injected with Thorotrast and (b) in a Swiss 51 mouse injected with Micropaque. Both tumors are similar in appearance, with same vascular characteristics as in transplanted breast tumors (Cf. fig. 3). 'Brushes' are again seen.

variable caliber densely arranged in a parallel fashion with 'brush-like' structures were noted. They surrounded the tumor lobules and formed multiple tufted areas throughout the tumor.

Spontaneous adenocarcinomas of the breast

Thirteen spontaneous adenocarcinomas of the breast in C3H mice were examined with Thorotrast and 1 spontaneous breast tumor in a Swiss and 1 in a C3H mouse with Micropaque. Only 2 of the 14 spontaneous tumors in

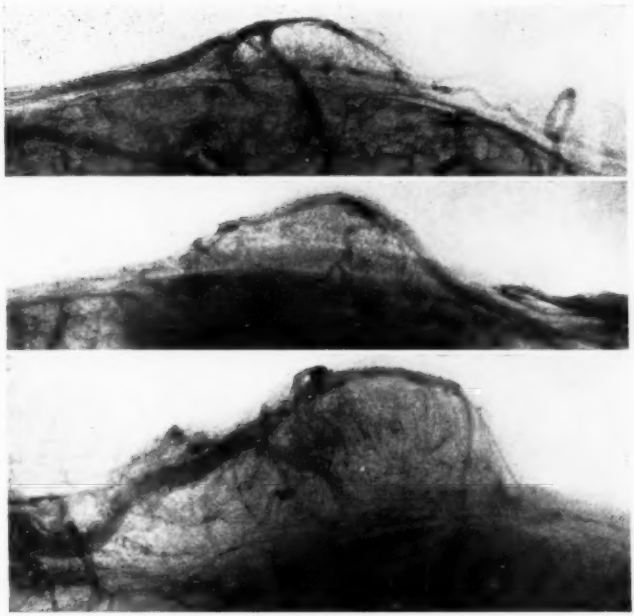

Fig. 5. Three examples of growth study of transplanted breast tumors. The characteristics of the vascularity appear early and do not seem to change with growth; the similarity with the vessels in figs 3 and 4 is striking.

C3H mice failed to show the same vascularity evident in the transplanted breast tumors. The Micropaque injected breast carcinoma in the Swiss 51 mouse resembled the other 12. All tumors showed similar 'brushes', lobulation, and vascularity. The vessels entered the neoplasm perpendicularly and did not exhibit the parallel arrangement beneath the tumor evident in the transplanted breast tumors (Fig. 4). The demarcation between the normal subcutaneous tissue and the tumor was not sharp and suggested infiltration.

Lymphosarcoma

Twenty-five C3H mice were studied with Thorotrast and 4 with Micropaque (from our Cancer Research Division). The tumors grew rapidly, spread parallel to the surface of the body, and were not sharply demarcated from the normal subcutaneous tissue. The tumor vessels injected with Thorotrast were generally smaller than in the other neoplasms studied and tended to run parallel with the body surface (Fig. 6). Fine vascular structures arose perpendicularly from

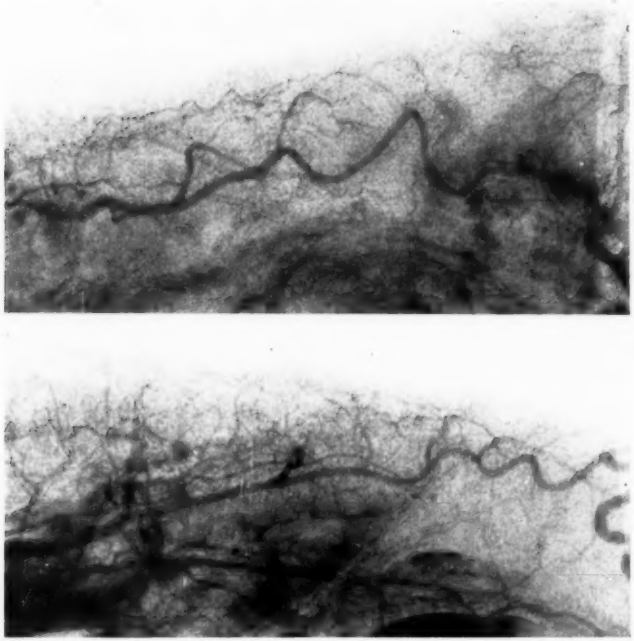

Fig. 6. Two representative Thorotrast injections of lymphosarcoma. Parallel arrangement of vessels forming layers.

these vessels and ran toward the surface. The large veins draining the tumors were somewhat tortuous but had the same parallel orientation to the surface of the body. In the tumors injected with Micropaque only the arteries were visible and these also ran in a parallel direction to the body surface; no fine vascular structures were identified. Conclusions regarding the presence or absence of channels larger than capillaries cannot be drawn from this small series.

Sarcoma 37

Fourteen tumors in DBA 1 mice (from Jackson Memorial Laboratory) were studied with Thorotrast and 3 with Micropaque. The contrast medium used did not alter the angiographic appearances. The vessels below the tumor ran parallel to the surface of the body and those in the tumor were numerous, markedly irregularly distributed, and large. There were numerous ill-defined areas ('lakes') filled with contrast medium throughout the neoplasms. Some of the tumors had vessels running perpendicularly into large superficial vascular

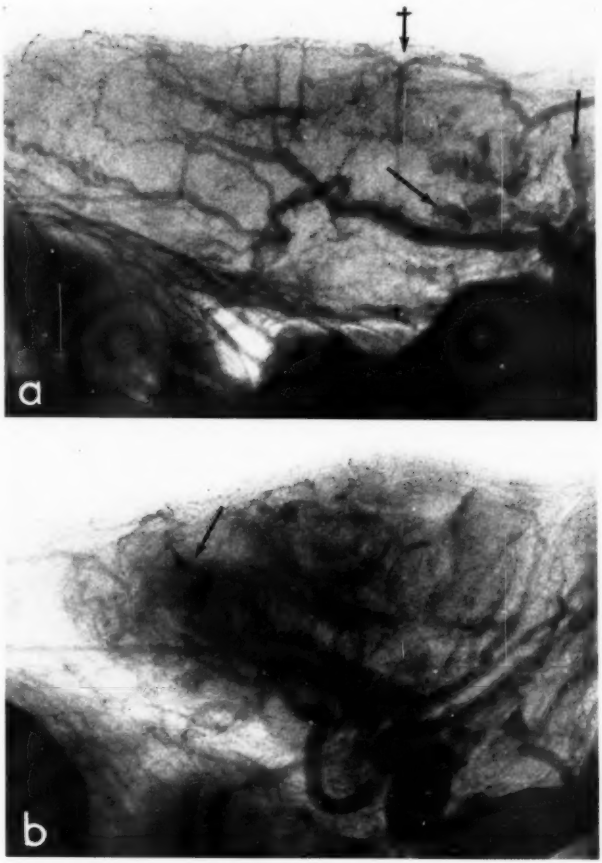

Fig. 7. Two examples of sarcoma-37. Irregular arrangement of vessels, numerous 'lakes' (arrows). In (a) vascular 'candelabra' arrangement (↔).

channels lying parallel to the body surface. We called this arrangement 'candelabra' (Fig. 7).

Rhabdomyosarcoma

Twenty tumors in C3H mice were studied with Thorotrast, and 8 with Micropaque (from our Cancer Research Division). The tumors were not sharply demarcated and the supplying vessels entered them perpendicularly. When studied with Thorotrast the vessels in the tumors were numerous, and

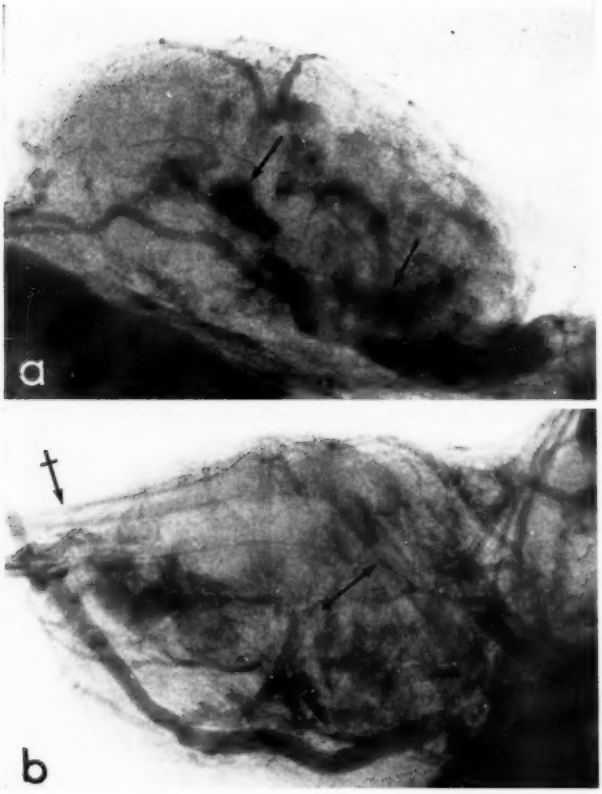

Fig. 8. Examples of transplanted rhabdomyosarcomas. The irregular arrangement of vessels is similar to that seen with sarcomas (cf. fig. 7). Numerous 'lakes' (arrows). a) Subcutaneous inoculation, and b) intramuscular inoculation in thigh, tibia (↔) and femur (arrow marked with star in the middle of the tumor) did not differ in vascular arrangement.

irregular. 'Lakes' were present in 17 of the 20 tumors studied. The arrangement of the vessels was markedly irregular. The vessels were generally larger but similar to those seen in sarcoma-37; the differentiation is usually not possible by angiography (Fig. 8).

Studies with Micropaque in which the injection was entirely on the systemic arterial side presented a completely different angiographic pattern. Only arteries were seen in the tumor and no filled veins nor 'lakes' were present. Although the general arrangement of the vessels was still irregular, the angiographic appearances differed significantly from those obtained by injection

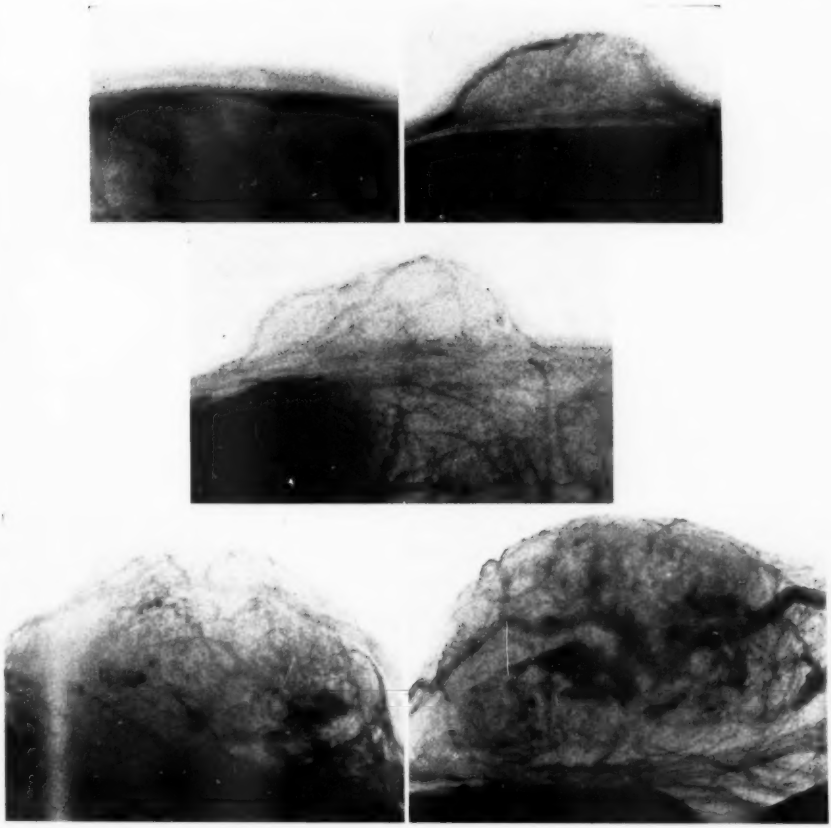

Fig. 9. Illustrative angiograms from a growth study of rhabdomyosarcomas (Cf. fig. 8).

with Thorotrast. No definite conclusions can be drawn from such scanty material but the problem of arteriovenous communications in rhabdomyosarcomas needs further investigation by microangiography.

Growth studies

Angiography was also performed in tumor-bearing mice at various stages of tumor growth. It was desired to establish the angiographic changes that occur with growth and determine the time when a characteristic angiographic pattern is evident. Three transplantable tumors were selected for this purpose: rhabdomyosarcoma, adenocarcinoma of the breast, and squamous cell car-

cinoma of the skin. Equal transplants of the tumor were inoculated into large groups of mice and angiography was performed by the method described. Rhabdomyosarcoma-bearing mice were studied at two-day intervals starting on the third day after the transplantation of the tumor and were carried through the twenty-sixth day. Breast tumor growth studies were started on the seventh day following transplantation. The examinations were performed every third day and were carried through the twenty-eighth day. The group of Swiss 51 mice that was inoculated with squamous cell carcinomas was studied at four-day intervals in the beginning of the study and later at two-day intervals. The time of study was between the seventh day and the twentieth day after transplantation.

The basic features of the vascular arrangements appeared early and were unchanged during growth (Figs 1, 5 and 9). As squamous cell carcinomas became cystic they showed fewer vessels. Similar studies are being conducted on other tumors.

Conclusions

Tumors of mice studied by angiography appeared to have characteristic vascular arrangements, these being similar in those having common histologic features, such as sarcomas-37 and rhabdomyosarcomas or, to a lesser extent, hepatomas and breast carcinomas. Spontaneous breast carcinomas presented the same angiographic appearances as transplanted mammary gland carcinomas. Spontaneous and transplanted carcinomas of the breast, lymphosarcomas and rhabdomyosarcomas had specific and characteristic angiographic appearances in spite of the fact that they all grew in the same strain of mice (C3H). There was no definite difference in the vascularity of carcinomas of the breast whether they were present in C3H or Swiss 51 mice. Growth studies of rhabdomyosarcomas, carcinomas of the breast, and squamous cell carcinomas indicated that their vascular arrangement started early in the course of their growth and did not change. Rhabdomyosarcomas presented the same vascular appearances whether transplanted subcutaneously or intramuscularly. More work is needed to study arteriovenous communications in the tumors in order to correlate the minute histologic and angiographic appearances, and to clarify the nature of the 'lakes', 'brushes', and lobulation. Microangiographic investigations of tumors in mice are being conducted.

Acknowledgement

We wish to express our thanks to Dr Valentina Suntzeff for her invaluable help and suggestions and for supplying some of the tumor-bearing mice, to Dr Michel Ter-Pogossian for his guidance in solving many of the technical problems, and to Mr. Cramer Lewis who provided the photographic enlargements and reproductions. The investigation was supported by a grant from the American Cancer Society.

SUMMARY

A liminary report of angiographic studies on 171 adult tumor bearing mice is presented. Char teristic angiographic appearances of various tumors were established and are descr d. The vascularity of transplanted adenocarcinomas of the breast, rhabdomyosarcomas and amous cell carcinomas were examined at specified intervals during their growth.

ZUSAMMENFASSUNG

Ein orläufiger Bericht über angiographische Studien an 171 ausgewachsenen tumorkranken Mäus wird vorgelegt. Charakteristische angiographische Befunde verschiedener Tumoren wurd festgelegt und werden beschrieben. Der Gefässreichtum transplantierter Adenokarzi me der Brust, von Rhabdomyosarkomen und Plattenepithelkarzinomen wurde mit besti ten Intervallen während ihres Wachstums untersucht.

RÉSUMÉ

Les uteurs présentent une note préliminaire sur l'étude angiographique de 171 souris adult porteuses de tumeurs. Ils ont établi et décrivent les aspects angiographiques caractéristi es de diverses tumeurs. Ils ont examiné la vascularisation d'adénocarcinomes du sein, de rha domyosarcomes et d'épithéliomas malpighiens différenciés transplantés, à des intervalles déterminés au cours de leur croissance.

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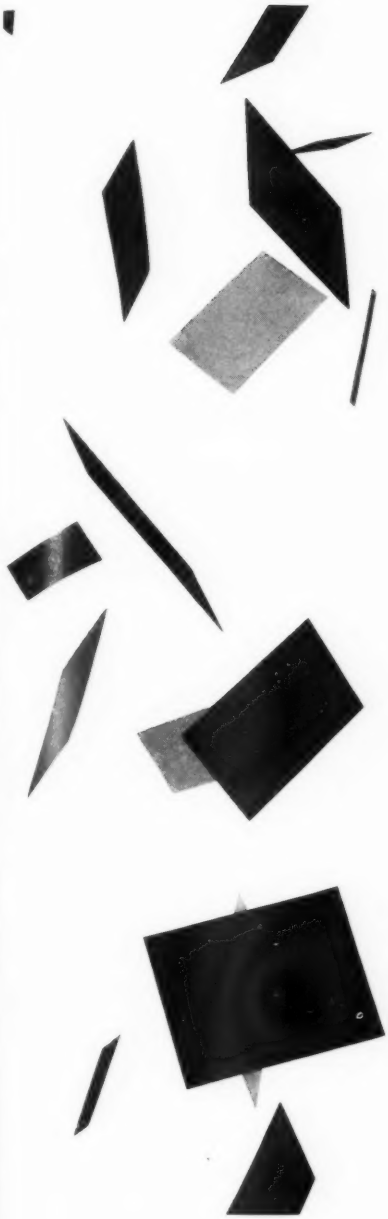

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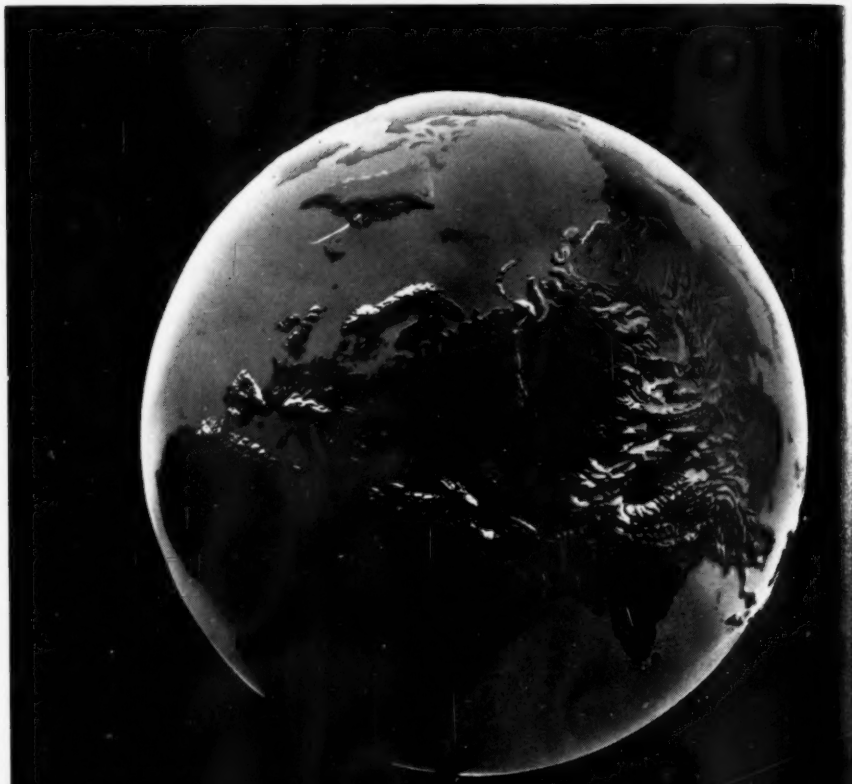

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INFLUENCE OF CERTAIN PHYSICAL FACTORS ON THE RADIOGRAPHIC DEMONSTRATION OF CHOLESTEROL GALLSTONES

by

PEKKA VIRTAMA

Roentgen examination of the gallbladder is a reliable method and one in which the roentgenologic and operation findings are in agreement in more than 90 per cent of cases. The roentgen technique is well established, but the exact role played by certain physical factors in demonstration of small gallstones, particularly the concentration of iodine in the gallbladder and the tube voltage used, is not quite clear. HORNYKIEWYTSCH and STENDER (1953) recommended an exposure of 120 to 200 mAs at 60 to 65 kV in intravenous cholegraphy, while COCCHI (1953) and WEGELIUS et coll. (1954) advocated the use of a high-voltage technique in cholecystography. SAMUEL (1960) expressed the fear that the high density produced by certain new cholegraphic contrast media might not be entirely advantageous because small stones might be obscured. The introduction of these new compounds would therefore appear to justify a re-appraisal of the radiographic technique with special regard to the importance of the tube voltage in the demonstration of small gallstones.

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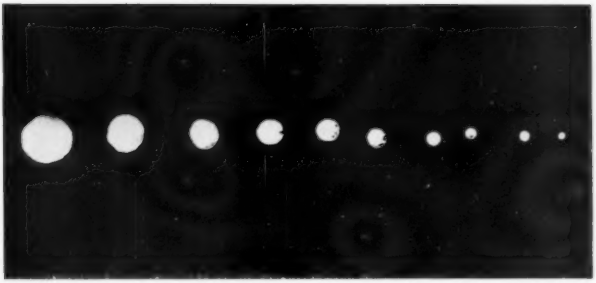


Fig. 1. Artificial cholesterol stones used in the experiments.

Material and Methods. The equipment used was experimental. A large perspex tray, 18 × 34 × 35 cm in size and filled with water, was used as a soft tissue phantom; the absorbing mass of the phantom was in effect considerably larger than that of a medium-sized patient. A long square perspex tube, measuring 2.5 × 2.5 × 25.0 cm, acted as a gallbladder and was filled with various concentrations of cholegraphic contrast media.

The smallest gallstones are usually non-calcified cholesterol or cholesterol pigment stones (Epprecht et coll. 1953, and others). Suitable artificial stones were made from 75 % cholesterol and 25 % gelatine mixed at 65 to 70° C, formed into rounded pellets of various sizes, and surface-hardened by being steeped in 10 % formalin for 12 hours. The absorption qualities of the artificial stones were compared with those of pure cholesterol by examining them at the voltages used in the course of this study with equal amounts of cholesterol. No difference was evident.

The diameters of the stones examined were 1.0, 2.0, 2.5, 3.0, 4.0, 4.5, 5.0, 6.0, 7.0 and 10.0 mm. They were fixed on a perspex plate with perspex cement

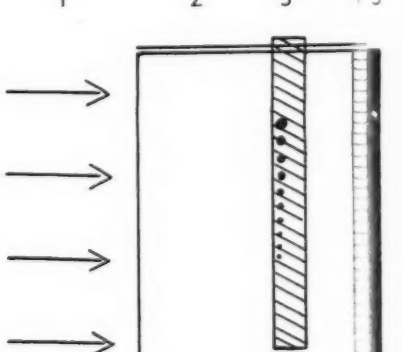


Fig. 2. Experimental arrangement. 1 — Roentgen rays, 2 — Perspex tray filled with water, 3 — Perspex tube containing contrast medium and cholesterol stones, 4 — Cross-grid, 5 — Cassette with film.

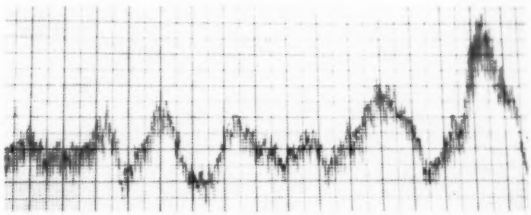


Fig. 3. Densitometric curve recorded from image in fig. 6d. Concentration of Biligrafin 5.0 g/100 ml; kV 50, mAs 2 000.

(Tensol cement ICI), and the plate with the stones (Fig. 1) was dipped into the contrast medium in the perspex tube which was placed in the water in the large perspex tray (Fig. 2).

The contrast media examined were Biligrafin (Schering), Solu-Biloptin (Schering) and Bilijodon-Natrium (Leo) which were diluted with water to the following concentrations: 0.2, 0.5, 1.0, 2.0, 5.0, and 7.0 g/100 ml.

A three-phase roentgen apparatus, the Siemens 'Tridoros', was used. The roentgen tube was fitted with two foci, the effective size of which were 0.3 and 1.0 mm^2 as given by the manufacturers. FFD 75 and 150 cm; field sizes 9×12 and 18×24 cm. A stationary cross-grid was used. The voltages were 50, 60, 70, 80, 90 and 100 kV. The mAs values were adjusted so as to give a background density of 1.2 density units, as produced by a 18 cm thick water layer. The highest mAs value used was 2 200 at 50 kV. Kodak's Blue Brand roentgen film and Siemens' Rubin fine grain intensifying screens were employed throughout the study; the films were developed in DX 80 developer at 20° C with intermittent manual agitation for 4 min. Fixing, washing and drying were carried out in the usual way.

To obviate any subjective bias in judging the visibility of the stones, the films were analysed with the aid of a doublebeam recording densitometer (Joyce & Loebl & Co Ltd, Newcastle upon Tyne, England). A scanning line crossing the roentgen images of the stones was recorded from the films. The ratio of the lever connecting the densitometric table with the recording pen was 1 to 2, so as to give a $\times 2$ enlargement. Each stone caused a certain deflection in the densitometric curve (Fig. 3). The height and the width of the deflection caused by a just-detectable stone was determined with the aid of several blind tests by five independent observers. It was thus possible to register the smallest stone detectable from the densitometric curves.

Results

The diameters of the smallest stones detectable in various conditions are seen from Table 1. The arithmetic means of the values obtained with different concentrations of the contrast media and at the voltages used were calculated.

Table 1

Effect of kV and concentration of various contrast media on the demonstration of gallstones

Concentration	kV	Diameters (mm) of smallest stones discernible with different media			
		Biligrafin	Solu-Biloptin	Bilijodon-Natrium	M[illegible]n
0.2 g/100 ml	50	3.0	3.0	3.0	[illegible]
	60	3.0	3.0	3.0	[illegible]
	70	3.0	3.0	3.0	[illegible]
	80	4.0	4.5	4.5	[illegible]
	90	4.5	4.0	4.5	[illegible]
	100	5.0	4.5	5.0	[illegible]
0.5 g/100 ml	50	2.5	2.0	2.0	[illegible]
	60	2.5	2.5	2.5	[illegible]
	70	3.0	3.0	3.0	[illegible]
	80	3.0	3.0	4.0	[illegible]
	90	3.0	4.0	4.0	[illegible]
	100	4.5	4.5	4.5	[illegible]
1.0 g/100 ml	50	2.0	2.5	2.5	[illegible]
	60	2.5	2.5	2.5	[illegible]
	70	2.5	2.5	2.5	[illegible]
	80	3.0	3.0	4.0	[illegible]
	90	4.0	4.0	4.0	[illegible]
	100	4.5	4.5	4.0	[illegible]
2.0 g/100 ml	50	2.0	2.0	2.0	[illegible]
	60	2.0	2.0	2.0	[illegible]
	70	3.0	3.0	2.5	[illegible]
	80	3.0	3.0	3.0	[illegible]
	90	4.0	3.0	3.0	[illegible]
	100	4.0	4.5	4.5	[illegible]
5.0 g/100 ml	50	1.0	1.0	1.0	[illegible]
	60	1.0	1.0	1.0	[illegible]
	70	2.0	2.0	2.0	[illegible]
	80	2.5	2.5	2.5	[illegible]
	90	3.0	3.0	2.5	[illegible]
	100	4.0	4.0	4.0	[illegible]
7.0 g/100 ml	50	1.0	1.0	1.0	[illegible]
	60	1.0	1.0	1.0	[illegible]
	70	2.0	1.0	2.0	[illegible]
	80	2.5	2.0	2.0	[illegible]
	90	3.0	3.0	3.0	[illegible]
	100	3.0	4.0	3.0	[illegible]

The mean diameters of the smallest stones detectable were plotted against the tube tension (Fig. 4) and the concentration (Fig. 5). The smallest stone, 1 mm in diameter, was discernible at 50 and 60 kV in concentrations of 5.0 g/100 ml or more. The size of the smallest stone demonstrable at 50 to 60 kV was about half the size of the stone visible at 100 kV in the same concentration. The effect of the concentration of the contrast medium was especially marked

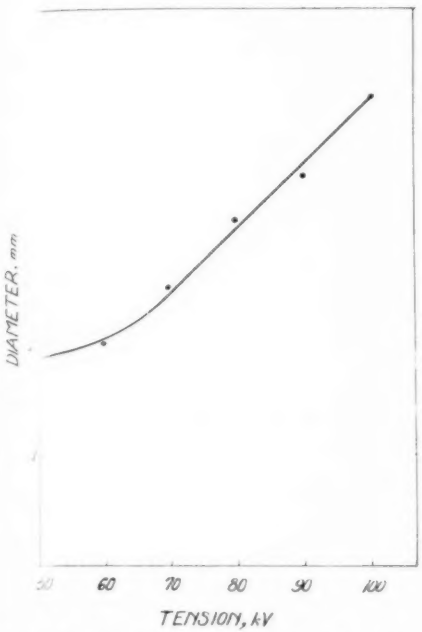


Fig. 4. Arithmetic means of diameters of smallest stones detectable at various tube tensions.

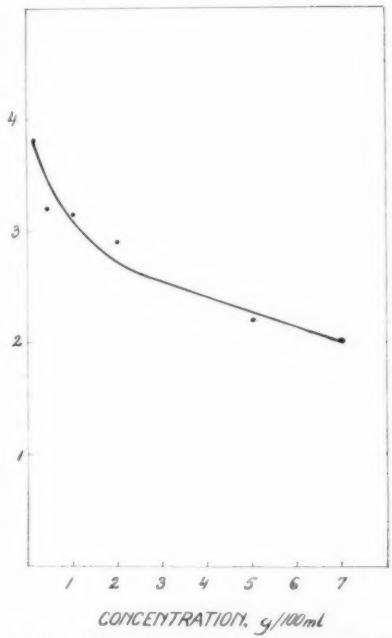


Fig. 5. Arithmetic means of diameters of smallest stones detectable in various concentrations of contrast media.

in low concentrations, and the detectability of the stones was considerably impaired in concentrations less than 1.0 g/100 ml.

The results were analysed according to standard statistical methods. A highly significant correlation between the size of the smallest stone detectable and the concentration of the contrast medium and the voltage used was found at the level of $P < 0.001$. This means that the detectability of the stones was impaired by low concentration of the contrast medium and by high voltage (Figs. 4, 5 and 6). There were no significant differences in this respect between the contrast media examined.

Effects of the focal size of the roentgen tube, the FFD, and the field size were analysed in the same manner. The results obtained by the statistical analysis are given in Table 2.

Discussion

All gallstones cannot be demonstrated roentgenologically. There is a limit size in cholesterol concretions detectable, which is dependent on the radiographic technique used. It is obvious from the results obtained that factors

Table 2

Effect of field size, focal size and FFD on demonstration of gallstones

		Mean diameter (mm) of stone visible		Mean diameter (mm) of stone visible	P
Field size	18 × 24 cm	3.7	9 × 12 cm	3.1	0.02
Focal size	1 × 1 mm	4.1	0.3 mm²	3.3	0.01
FFD	150 cm	3.3	75 cm	3.7	..

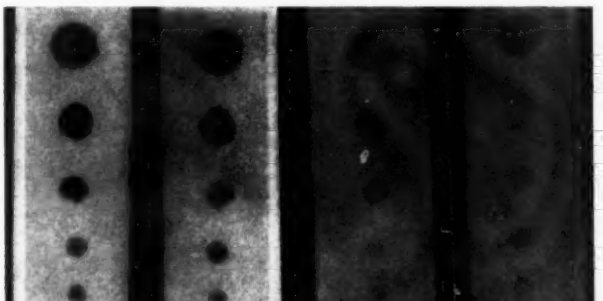
increasing radiographic definition and contrast improve the detectability of small cholesterol stones. The following conclusions may be drawn:

A fine focal spot, 0.3 mm in diameter, significantly improves the detectability of cholesterol concretions by decreasing the geometrical blurr as compared with 1 mm of focal spot in diameter.

A small field size (9 × 12 cm) increases the radiographic contrast (MORGAN 1946) thus also increasing the detectability of gallstones.

Low voltage and high concentration of iodine in the gallbladder improve the results significantly by increasing the radiographic contrast.

A high voltage technique is advantageous in the roentgen examination of the gastrointestinal tract with barium sulphate owing to the increased penetrability of the roentgen rays, as shown by GIANTURNO (1950) and BÜCHER (1952). However, this does not wholly apply to examinations with iodine-



a b c d

Fig. 6. Roentgen images of phantom gallbladder: a), b), and c) at a concentration of 5.0 g/100 ml Biligrafin and with tube tensions of 50 kV, 70 kV, and 100 kV, respectively; d) at a concentration of 0.2 g/100 ml Biligrafin and tube tension 50 kV.

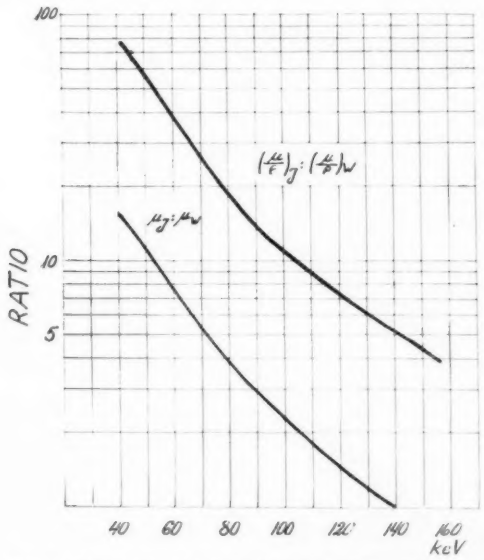


Fig. 7. Ratio between linear absorption coefficients (μ) and mass absorption coefficients ($\frac{\mu}{\rho}$) of iodine and water at different monochromatic radiation energies.

containing compounds, because of their absorption characteristics. As seen from Fig. 7, the linear absorption coefficient of iodine (MORGAN & CORRIGAN 1955) is very near to that of water at about 150 kV.

Only about 5 per cent of the orally administered diiodo contrast medium is excreted in the bile, this becoming 36 per cent with intravenously administered Biligrafin (BILLION 1954). The concentration of the former in the gallbladder does not therefore exceed 0.3 g/100 ml, while the concentration of the latter may be as high as 6 to 7 g/100 ml (FROMMHOLD 1953). It is apparent that voltages higher than 70 to 80 kV cannot be recommended in oral cholegraphy, while in intravenous examinations voltages up to 100 kV give approximately the same result owing to the high concentration of iodine in the gallbladder, as seen from Table 1. Furthermore, in uncertain cases when gallstones are probable but are not confirmed, an intravenous examination rather than a further oral examination is advisable. This is particularly valid when the size of the subject requires a large exposure, because the higher concentration of the contrast medium renders it possible to use a relatively high kilovoltage. Very high mAs values are not feasible in practice by reason of the increased blurring and loading of the roentgen tube caused by long exposure times.

Small cholesterol concretions may obviously be obscured by underexposure of a dense gallbladder. However, with the aid of the increased density produced by the new triiodo compounds, the results of cholegraphy may further be improved, provided that the radiographic technique is adjusted so as to give maximum contrast and definition.

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SUMMARY

The visibility of artificial cholesterol stones was investigated with the aid of phantom experiments. The diameter of the smallest stone discernible was 1 mm. The best results were obtained at relatively low voltages and high concentrations of contrast media. Factors increasing the radiographic contrast and definition improved the possibilities of demonstrating the stones.

ZUSAMMENFASSUNG

Die Sichtbarkeit künstlicher Cholesterinsteine wurde mit Hilfe eines Phantomexperiments untersucht. Der Durchmesser der kleinsten erkennbaren Steine war 1 mm. Die besten Resultate wurden bei relativ niedrigen Spannungen und bei hohen Konzentrationen des Kontrastmittels erzielt. Faktoren, welche den röntgenographischen Kontrast und die Auflösung steigern, verbesserten die Möglichkeiten, die Steine zu demonstrieren.

RÉSUMÉ

La visibilité de calculs de cholestérol artificiels a été étudiée par des essais avec un fantôme. Le plus petit calcul visible avait un diamètre d'un millimètre. Les meilleurs résultats ont été obtenus avec des tensions relativement basses et une forte concentration de moyen de contraste. Les facteurs qui augmentent le contraste radiographique et la définition ont amélioré les possibilités de mettre les calculs en évidence.

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FROM THE FORMER CHIEF (W. HONDIUS BOLDINGH) OF THE X-RAY DEVELOPMENT LABORATORY OF N. V. PHILIPS' GLOEILAMPEN-FABRIEKEN, EINDHOVEN, HOLLAND.

QUALITY AND CHOICE OF POTTER BUCKY GRIDS
PART VI

by

W. HONDIUS BOLDINGH

VI. Exposure data for various grids

For the preceding articles in this series the reader is referred to Parts I—III (BONENKAMP & HONDIUS BOLDINGH 1959) and Parts IV—V (HONDIUS BOLDINGH 1961).

Ever since the advent of medical radiography exposure tables for the various parts of the body have been employed. These tables originally comprised data suitable for a particular installation, and not until reliable control of the voltage had been achieved did the tables become more universally applicable. Reproducible and comparable voltages were obtainable after World War II, but even then only in those cases in which adequate allowance for any mains voltage drop had been made.

Although most exposure tables indicate when a grid should be employed, they generally contain no detailed specification for the grid itself; in some charts a factor for grids of given ratios may be indicated by which the basic mAs values (without grid) should be multiplied. Information of this kind would be of value only if it were a fact that the factors were the same for all grids of the same ratio, irrespective of object and exposure conditions. But such is not the case. For a grid of a given ratio, the Bucky factor depends to a large extent on the strip density (number of strips per cm), the thickness of the object, the width of the beam, and the voltage. This is clearly shown in Table 1, in which

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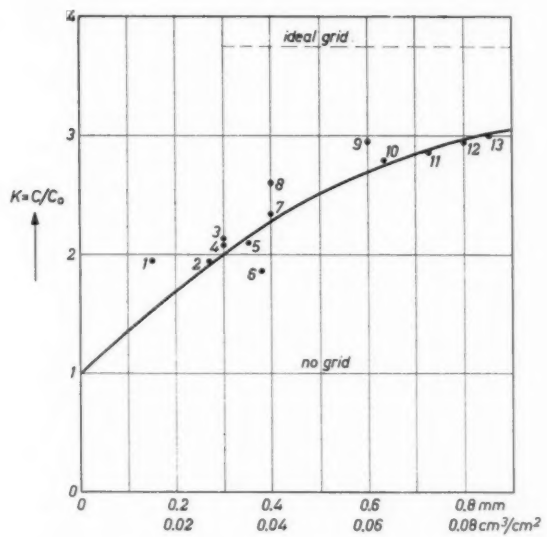

Diagram 1. Contrast-improvement factor K_{100} (100 kV d. c., 20 cm H_2O), as a function of the lead content.
(This graph appears also in Vol. 55, p. 232, of Acta Radiologica.)

the Bucky factors, B, are given for light and heavy grids at 60, 100 and 200 kV; the factors have been determined with a wide beam in water phantom thicknesses of 10, 20 and 30 cm.

Table

Bucky factors of various grids for different tube voltages and different phantom thicknesses

	10 cm H_2O	20 cm H_2O	30 cm H_2O
60 kV	2.3—3.5	2.5—6.0	3.7—7.2
100 kV	2.1—3.2	2.5—5.0	3.0—6.6
200 kV	1.9—2.9	2.1—4.3	2.6—5.1

Other charts may prescribe voltage increase for grids of given ratios, but such recommendations are unsuitable for nearly the same reasons as given above. It is also a fact that no general value can be attached to the recommendation to employ coarse or fine grids, since there are grids that require the same exposure times whether they contain relatively few (25), or many (40) strips per cm.

It is perhaps surprising that the various recommendations for the use of grids have not introduced more difficulties in actual practice, but this may be

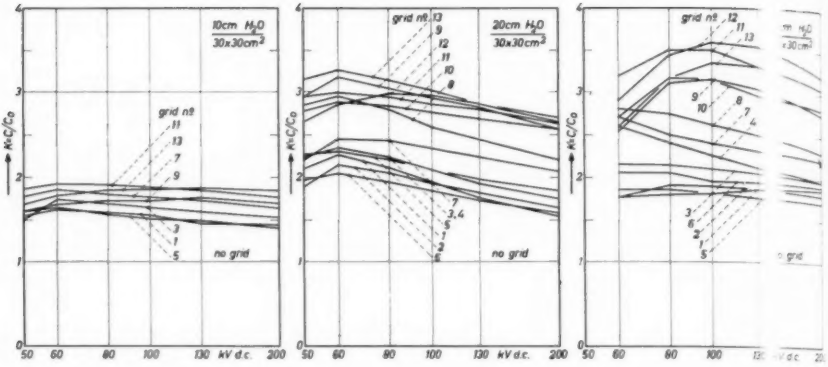

Diagram 2. Contrast improvement factor as a function of the tension.
(These graphs appear as diagram 3 in Vol. 55, p. 231, of Acta Radiologica.)

due to the fact that, as long as the various types of grids were of the same low ratio, the exposure data did not differ much. A great variety of grids of different types and designs have, however, recently become available, and many roentgen couches and stands are designed for use with interchangeable grids, so that the radiologist may to-day be forced into the same situation as in earlier days: as soon as he brings a new type of grid into use he may have to compile a new exposure table. An indication of the ratio of a grid will not be sufficient, even less so than in earlier days, for an adequate determination of the required exposure data.

The *contrast improvement factor*, introduced in Part V (HONDIUS BOLDINGH 1961) can help us out of this difficulty. It may be recalled that this factor, K, is determined by the quotient when the contrast obtained with grid is divided by the contrast without grid:

$$K = C/C_o,$$

determined under standard conditions. This factor is of value not only because it constitutes a direct measure of the contrast-improving capacity of the grid, but also because it may be correlated in a simple way to the exposure data.

As may be seen from Diagrams 1 and 2 (reproduced from Diagrams 3 and 4 in Part V, pp 231 and 232), the contrast improvement factors for six of the thirteen grids, measured at 100 kV in a 20 cm water phantom (K_{100}) differ only slightly, their values being 1.85, 1.95, 1.95, 2.10, 2.10, and 2.10, respectively. As was also mentioned in Part V, differences of a few tenths in K_{100} are barely perceptible and thus of little significance in medical practice. These six grids belong to the group of light grids, with lead contents between 0.015 and 0.038 cm^3/cm^2, i.e. 0.15 to 0.4 mm in round figures. However, this is not the only

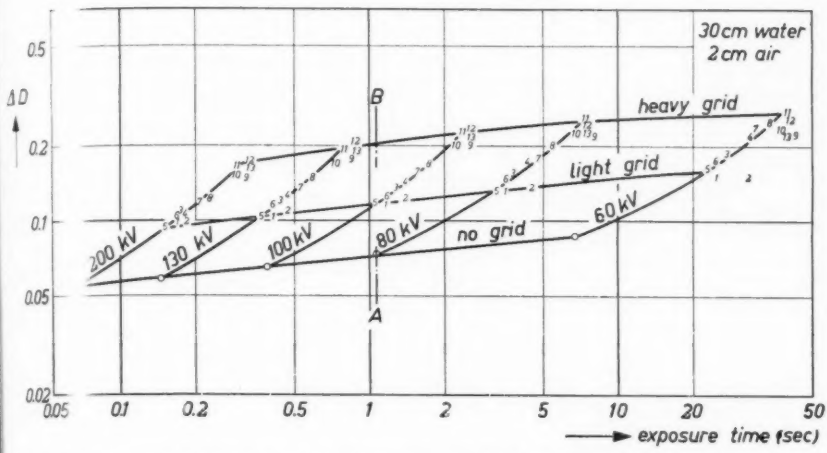

Diagram 2. Contrast ΔD as a function of exposure time from 60 to 200 kV. Bottom line, no grid; second line, lightest grid; top line, heaviest grid. Numbers 1 to 13 correspond to the grids used in the measurements, numbered in sequence of their lead content.
(This graph appears also in Vol. 52, p. 151, of Acta Radiologica.)

property that these grids have in common. As may be seen from Diagram 3 reproduced from Diagram 1 in Part II, p. 151), the exposure times at the same voltage, tube load, and film blackening, even with a 30 cm water phantom, do not differ much from a mean value. The fact that the results with all these grids are in conformity could offer an explanation why only vague indications for the use of grids are given in most exposure tables, as they may have been derived from measurements with grids perhaps varying in type, but all belonging to the group of 'light' grids.

As appears from Table 1 and Diagram 3, heavier grids may require exposure times twice as long as those required for lighter grids at the same voltage. This is not a constant factor, however, and such a big increase in the exposure time is, moreover, often unacceptable. It was stated previously (Part I, p. 488) that the requisite increase in exposure time may be compensated for by a voltage increase, and then only a small part of the contrast improvement need be sacrificed. Now it is a fortunate fact, based on empirical observations, that these voltage increases depend to a considerably smaller degree than the Bucky factor on the object thickness, and that within reasonable limits they are simply and linearly related to the contrast-improvement factor K_{100}, particularly so if cross-grids be excluded from the comparison.

The measurements with eleven linear grids, using 10, 20 and 30 cm water phantoms are given in Diagram 4, the required voltage for exposures with

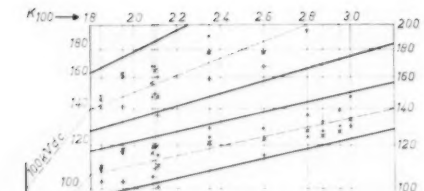

Diagram 4. Voltage as a function of the contrast-improvement factor K_{100} for equal exposure times, tube load and film-blackening for eleven linear grids (vertical lines) at different thicknesses of a 30 × 30 cm² water phantom.

Denotations: × 10 cm water phantom
. 20 cm » »
— 30 cm » »
– – – – Average for all object thicknesses
——— Tolerance lines corresponding to 25 % shorter and longer exposure times than the average values.

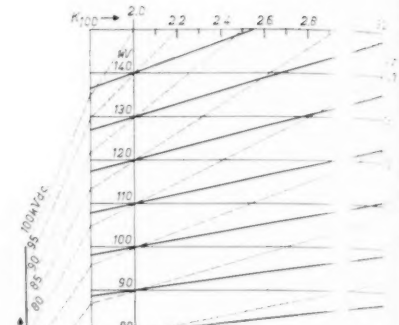

Diagram 5. Voltage (kV) as a function of the contrast-improvement factor of linear grids for given exposure times and film blackening. The averages for all object thicknesses are indicated by – – – – for equal tube load (kW) and ——— for equal tube current (mA and mAs).

grid being given as a function of K_{100} and compared with the values obtained at 50, 60, 80, and 100 kV without grid (on the extreme left). The graph in Diagram 4 has been constructed on the basis of the measurements described in the earlier parts, in which the Bucky factors and the relationship between mAs and kV were obtained with equal tube load and the same film blackening.

As regards the deviations from the straight-line average of the individual values (denoted by the symbols ×, ·, and —) for the three different thicknesses (broken lines in Diagram 4) it should be remembered that voltage differences corresponding to a reduction or increase by about 25 % of the mAs values cause no appreciable difference in film blackening. This tolerance is indicated by the fully-drawn lines in Diagram 4.

The (approximate) independence of the voltage increase with respect to object thickness may be explained as follows: Although the Bucky factor requiring compensation might be greater with thicker objects, the requisite voltage increase will be less because of the fact that when radiation passes through a thicker object it becomes 'harder', due to filtration

When therefore the value of K_{100} of a heavy grid is known, it becomes possible with the aid of a simple, rectilinear graph (Diagram 4) and an exposure table compiled for light grids to determine the voltage to be applied with a heavy grid in order to attain equal film blackening with the same exposure times and tube loads as given for the light grids. Diagram 5 is even more suitable for this purpose, since lines are drawn from 50 to 140 kV for light grids (K_{100} = 2.0). For the sake of completeness, the corresponding voltages for exposures without grid are also indicated on the extreme left of this diagram.

The broken lines in Diagrams 4 and 5 apply to constant tube loads (isowatt), and are therefore suitable for operating the roentgen tube under full load. For the higher voltages required for exposures with a heavier grid, the tube current has to be reduced proportionally with the exposure time kept constant. It is evident, on the other hand, that if the voltage increase required for a heavier grid can be applied with the same tube current and yet without endangering the tube through overloading, a smaller voltage increase will suffice. In such a case the fully-drawn lines in Diagram 5 apply, while the interrupted lines are again applicable with constant tube load.

The graphs in Diagrams 4 and 5 are based on measurements with d. c. voltages. When pulsating voltages are used, the voltage increase required for exposures with grid will differ, but the differences in voltage increments between light grids, with K_{100} = 2.0, and heavier grids, e.g. with K_{100} = 3.0, are not so large as to require a different graph.

If the contrast-improving capacity were inscribed on all grids by the value of K_{100}, this would enable uniformity to be attained between exposure tables as far as the use of grids is concerned. Exposure data for grids could then always be based on those of light grids, with $K_{100} = 2.0 \pm 0.2$. For heavier grids Diagram 5 could then be applied, and the requisite voltage increases obtained by drawing vertical lines corresponding to the K_{100} value, for the grids in question.

Let us take, for example, the heaviest grid in our measuring series (13), which has the following specification:

$$\underline{n = 27/cm},\ R = 15,\ \underline{f_1—f_0—f_2 = 80—90—100\ cm}$$

$$P = 0.085\ cm^3/cm^2 = 0.85\ mm,\ \underline{K_{100} = 3.0}$$

Here the underlined values indicate all the properties that must be known for day-to-day work, the other values being only of secondary importance.

The vertical line (K_{100} = 3.0, to the right in Diagram 5) applies to this grid and indicates the recommended alternative tube voltages: instead of a light grid (K_{100} = 2.0) at 50, 60, 80, 100, 120 kV one should choose

54 65 90 119 152 kV for constant tube load
53 64 86 109 133 kV for constant tube current

SUMMARY

It is suggested that indications for the use of grids should be referable to 'light' gr . with $K_{100} = 2.0 \pm 0.2$ (determined under standard conditions). For obtaining roentgeno ams of equal blackening and with equal exposure times when using heavier grids, the valu of the higher tube voltages required may be obtained from a simple rectilinear graph that is itable for all object thicknesses.

ZUSAMMENFASSUNG

Der Verfasser schlägt vor, dass sich Angaben über den Gebrauch von Rastern auf .. ichte" Raster, mit einem Kontrastverbesserungsfaktor $K_{100} = 2.0 \pm 0.2$ (unter genormten Bed ngungen bestimmt), beziehen sollten. Zur Herstellung von Röntgenbildern mit gleicher Schw rzung und mit gleichen Exponierungszeiten bei Benutzung schwererer Raster können di dafür erforderlichen höheren Röhrenspannungen in einer einfachen geradlinigen grap ischen Tabelle, welche für sämtliche Objektdicken geeignet ist, abgelesen werden.

RÉSUMÉ

L'auteur propose que les indications pour l'emploi des grilles se rapportent au grilles 'légères', avec un facteur d'amélioration du contraste $K_{100} = 2{,}0 \pm 0{,}2$ (déterminé dans des conditions standard). Pour obtenir une radiographie de même noircissement avec le même temps de pose quand on utilise une grille plus lourde, on peut déterminer la tension plus élevée qui est nécessaire au moyen d'un simple graphique rectiligne valable pour toutes les épaisseurs d'objet.

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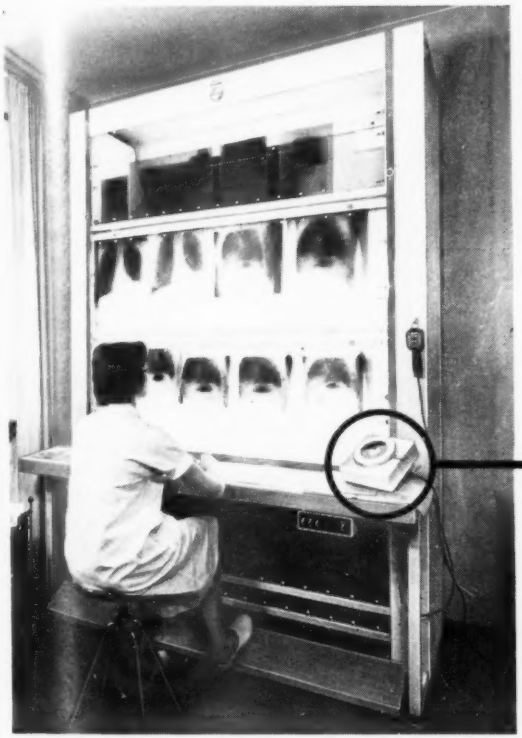

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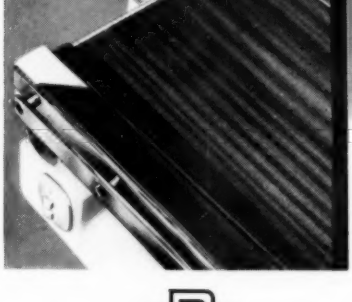

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FRO[illegible] THE DEPARTMENT OF GYNAECOLOGY (DIRECTOR: ASSOCIATE PROF. H.-L. KOT[illegible]MEIER), AND THE INSTITUTE OF RADIOPATHOLOGY (DIRECTOR: PROF. L. SANTESSON), RADIUMHEMMET, STOCKHOLM, SWEDEN.

CLINICAL ASPECTS OF DYSGERMINOMA OF THE OVARY

by

SAM BRODY

The ovarian dysgerminoma belongs to the group of germ-cell tumours (38). Much confusion has prevailed concerning the histogenesis and histopathology of tumours belonging to this group, and conflicting views have been expressed as to their structural interrelations. The histogenetic concept of TEILUM is now accepted by many authors for their classification.

The less differentiated tumours of this group, i.e. embryonal carcinoma, mesoblastoma (38), mesonephroma ovarii (30) and chorioepithelioma, are highly malignant and have an almost invariably fatal course (29). A dysgerminoma, on the other hand, exhibits a special and considerably more uniform histologic structure. From a clinical point of view as well it constitutes a special group within the germ-cell tumours, as is also the case with the corresponding seminomas of the testis. Although a dysgerminoma is a neoplasm displaying clearly malignant features in terms of proliferative capacity, destructive growth with infiltration of the pelvic organs, and a strong tendency to metastasize and recur, its degree of malignancy and response to various therapeutic procedures have been the subject of widely divergent opinions (15, 19, 25, 28). Thus the reported five-year survival rate varies from 27.3 to 66.6 per cent.

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Table 1

Age distribution and prognosis (60 cases)

Age in years	Number of patients	Five-year survival rate (%)	Recurrence ra (% of living
10—19	16	61	50
20—29	30	83	25
30—39	8	87	0
40—49	6	50	67

The reason for this considerable discrepancy in the prognosis has not previously been analysed in detail. Apparently several factors contribute to the conflicting therapeutic results. The rarity of the tumour, with mostly only a few cases investigated in the different series, has rendered difficult a proper evaluation of its clinical malignancy. Where larger series have been studied (15,19, 25, 28), the cases have usually been collected from reports in the literature. The heterogeneity of these materials as regards principles in diagnosis and treatment have necessarily affected the conclusions drawn as to prognosis.

There is one particular aspect which emphasizes the need for a proper evaluation of the degree of malignancy displayed by these tumours. The fact that dysgerminoma mostly occurs in young women, where preservation of the reproductive function is highly desirable, makes the decision as to the extensiveness of the therapeutic procedure to be undertaken a very important one. The question is whether there is justification for conservative treatment with preservation of the function of an apparently normal contralateral ovary, or whether the malignant potentialities of these tumours call for radical treatment in all cases. Conflicting opinions have been expressed as to the role of radiotherapy in the treatment. The problem of surgery alone or its combination with post-operative radiotherapy will therefore be discussed. Another question which will be considered in some detail is the genetic risk involved in conservative radiotherapeutic measures undertaken to avoid direct irradiation of an apparently normal ovary left after unilateral oophorectomy.

Material. This material comprises 60 patients, the earliest treatment dating back to 1921. The last patient was admitted to the hospital in 1959. It is an extension of the series presented by SANTESSON in 1947. As Radiumhemmet is mainly an institution specializing in radiotherapy, the cases admitted for treatment had been operated upon in other hospitals. In every instance the surgical specimen was subjected to pathologic examination. The final diagnosis, except in one patient who had been operated upon abroad, has been made by Prof. Santesson. It should be mentioned that in 3 patients only small parts of the tumours were sent for microscopic investigation. Sections from these parts contained pure dysgerminomatous structures.

Table 2

Clinical findings (60 cases)

	Number of patients	Per cent
Abdominal enlargement	18	30
Diffuse abdominal pain	19	32
Loss of weight	9	15
Abdominal mass	11	18
Acute onset	9	15
Pleural effusion	3	5
No symptoms or signs	8	13

Dysgerminoma is predominantly found in young patients. The age distribution in the present series is shown in Table 1. Twenty-seven per cent of the patients were under 20 and 77 per cent under 30 years of age.

The menarche usually occurred between 12 and 17 years of age. In the majority of cases the menstruations were normal. In 5 patients no bleeding had ever occurred. Of these patients 2 had genital malformations and 3 were under 14 years of age. In 4 patients meno-metrorrhagia was observed for various periods of time before the tumour was diagnosed. In 9 cases no menstrual data were available.

Thirteen patients had been pregnant once, twice, or three times before the appearance of the tumour. In 7 patients the tumour was diagnosed in connection with pregnancy. In one of these patients obstruction of the birth canal was caused by the tumour and the patient had to be delivered by caesarean section. In the other cases the diagnosis was made during the puerperium. All except one of these patients were primiparas. In an additional case a recurrence was diagnosed and operated upon 6 weeks after interruption of pregnancy.

Developmental changes in the genital sphere were observed in 5 patients. In one of these both ovaries and uterus were absent and in another there was an aplastic uterus. Two patients had hypoplastic uteri, one of these being bicornate. And in one patient a septate vagina and a lightly bicornate uterus was found.

Clinical picture

The tumour may be characterized by its insidious and undramatic development. In a large number of patients no discomfort was noticed and the neoplasm was accidentally diagnosed at routine check-up examinations. In the majority of cases the only complaint was enlargement of the abdomen, sometimes associated with diffuse abdominal pain and loss of weight. Some patients were aware of an enlarging firm mass in the lower abdomen.

In 9 instances the onset was sudden, with intense, constant unilateral pain, mostly in the lower abdomen and radiating down the thigh. These patients were sometimes in a state of shock and had fever. They were in the main

Table 3

Duration of symptoms or signs before diagnosis (60 cases)

	Number of patients	Per cent
≤ 1 week	9	15
1 week to 3 months	19	32
4 to 6 months	10	17
7 to 12 months	10	17
≥ 1 year	4	7
Asymptomatic	8	13

correctly diagnosed as having a twisted ovarian tumour or a spontaneous intra-abdominal perforation, but it was sometimes impossible to exclude the diagnosis of acute appendicitis before operation.

In one patient pleural effusion was found 11 months before the discovery of the dysgerminoma and in 2 other cases hydrothorax was noticed at the time of the diagnosis of the ovarian tumour. In none of these 3 patients were any other signs of pulmonary involvement present. In one of the patients, however, a metastasis in the supraclavicular region was found. No mention of the presence of ascites in any of these 3 patients was made in the reports of the operations. The frequency of the various presenting symptoms and signs is summarized in Table 2.

Owing to the lack of clear-cut and characteristic symptoms in most patients it is extremely difficult to obtain exact data as to the duration of the disease before its diagnosis. An approximate estimation of the duration of the symptoms and signs is, however, possible and, as is seen from Table 3, the progression of the disease is mostly comparatively rapid.

The right ovary was involved in 39 cases, the left ovary in 14, while bilateral involvement was observed in 7. The size of the tumours was in most cases impressive, and some weighing 3 to 4 kg were found. The tumour was adherent to other pelvic organs in 8 patients. Rupture of the tumour before or during the operation occurred in 5 patients, and torsion of the ovarian neoplasm was reported in 2 patients. Ascites was found in 5 patients.

Metastases were noted at the time of operation in 12 patients; in 7 of these bilateral ovarian involvement was evident (bilateral primary tumours or metastasis). Metastases were most commonly found in the omentum, the parametria and the peritoneum. Occasional spread to the lumbo-aortic and periportal lymphatics was reported (Table 4).

In the further course a sometimes marked tendency to recurrence and dissemination of the disease was observed. Lymphatic spread was the most common route. Involvement of the retroperitoneal lymph nodes along the iliac vessels and the aorta was usually observed early, but rapid involvement of the epigastric, mediastinal and supraclavicular nodes was also encountered. Haem-

Table 4

Localization of metastases (60 cases)

	Number of patients	Per cent
Retroperitoneal	5	8
Pelvic*	19	32
Abdominal*	13	20
Mediastinal*	3	5
Pulmonary	3	5
Hepatic	6	10
Ovarian	7	12
Skeletal	3	5
Supraclavicular	5	8
Inguinal	4	7

* Exact localization as to organ not possible.

genic dissemination, however, occurred as well. Metastases were found in the liver, lungs and ovary (metastasis or bilateral primary foci). In 3 patients involvement of the skeletal system was noted. A summary of the frequency of metastases in various locations is given in Table 4.

Treatment

All the patients referred to us had previously been operated upon in outside hospitals. A survey of the types of operation carried out is presented in Table 5 from which will be seen that both ovaries had been removed in 13 patients.

Fifty-six patients received post-operative radiation treatment, the remaining 4 patients not being referred to us until the diagnosis of a recurrence. Roentgen therapy was usually begun 3 to 6 weeks after the operation. Factors: 200 kV, 20 mA, FSD 40—80 cm, filter 0.5 mm Cu + 1.0 mm Al, daily dose 100—400 r (skin dose), one field per day, total dose per series 300—2 000 r. Particularly the early cases of this series, which were referred to us in the twenties and thirties, were almost consistently treated with small-to-moderate

Table 5

Survey of types of operation (60 cases)

	Number of patients
Unilateral oophorectomy	13
Unilateral salpingo-oophorectomy	25
Unilateral salpingo-oophorectomy + resection of contralateral ovary	7
Unilateral salpingo-oophorectomy + hysterectomy	2
Bilateral salpingo-oophorectomy	9
Bilateral salpingo-oophorectomy + hysterectomy	4

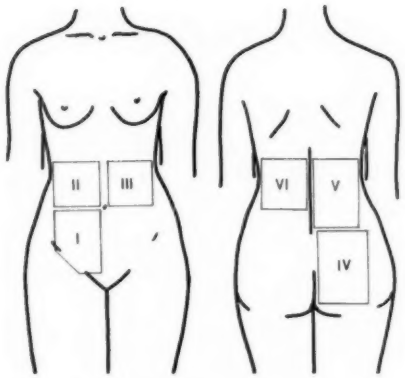

Fig. 1. Case 1. Anterior and posterior areas of roentgen irradiation.

doses of radiation. Later on, however, the treatment was given to each individual patient according to the extent of the disease at the time of operation and the nature of the latter, the clinical findings at the time of institution of roentgen therapy and the further course of the disease. In principle two types of initial roentgen treatment were given. In most patients of fertile age, in whom unilateral oophorectomy had been performed and in whom there was no indication of dissemination of the disease to the contralateral side at the time of operation or when beginning radiotherapy, no radiation was directed towards the remaining ovary. Moderate roentgen doses were given. This conservative program was carried out in 20 cases. To the remaining 40 patients in whom bilateral oophorectomy had been performed or in whom dissemination of the disease required more extensive radiotherapy, irradiation to the whole pelvis in addition to roentgen therapy to other areas was administered. It seems desirable, however, in addition to the above-mentioned general conditions, to give detailed data on a few patients who may exemplify various types of roentgen treatment.

Case reports

Case 1. 24-year-old nulligravida. No menstrual irregularities. Admitted to hospital February 1946 because of pleural effusion. Two liters of exudate removed in March; subsequent repeat pulmonary roentgen examinations were negative. An abdominal mass was found in December 1946. Last menstrual period at the end of that month. At operation a month later an encapsulated mass, weighing 700 g and originating from the right ovary, was removed. Unilateral salpingo-oophorectomy was performed. Referred to Radiumhemmet.

Roentgen therapy 27 January to 15 February: Three abdominal and corresponding dorsal areas (Fig. 1), field sizes varying from 150 to 200 cm². Irradiation given in sequence towards areas I to VI (Fig. 1), one field per day; three series, 150 to 300 r on each occasion, total dose 500 to 700 skin r per field. No direct irradiation towards the remaining ovary.

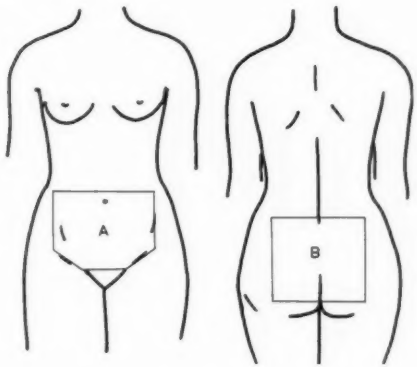

Fig. 2. Case 2. Anterior and posterior areas of roentgen irradiation.

Normal menstruations February to May 1947. After this time pregnant, with confinement in February 1948. Pregnancy and parturition without complications; normal child. Well at follow-up examinations. Pregnant for the second time in May 1954. Uncomplicated pregnancy and normal parturition and child. No signs of recurrence at repeated follow-up examinations. Last control September 1960.

Case 2. 44-year-old nulligravida. Primary amenorrhoea. Admitted to hospital January 1951 because of attacks of severe abdominal pain. The noteworthy observations were a vagina ending in a blind pouch, no cervix or uterus, and a hard, somewhat cystic pelvic mass. At operation a grapefruit-sized tumour on the left side was extirpated. No ovaries or uterus could be found. (A detailed report of the sexual abnormalities in this case has been given by MORRIS.) Referred to Radiumhemmet in March 1951. At that time no signs of progression of the disease.

Roentgen therapy 1951: Field A (400 cm², Fig. 2), 15 to 21 March, 100 r per day, total 600 r, and field B (500 cm² Fig. 2), 28 March to 3 April, 100 r per day, total 600 r.

At controls, completely well up to *April 1953* when a metastasis in the left supraclavicular region was found. Roentgen therapy: Field C (100 cm², Fig. 3), 17 to 22 April, 400 r per day, total 2 000 r. At examination on 6 June, 1953, there was no evidence of metastases.

Well at control examinations. On *15 October, 1953*, however, a mass over 10 by 15 cm in size was found in the left upper abdominal quadrant. Roentgen therapy: Field D (300 cm², Fig. 3), 15 to 20 October, 150 r per day, total 750 r, and field E (125 cm², Fig. 3), 21 to 23 October, 250 r per day, total 750 r. No evidence of this tumour was found at examination in December 1953.

Severe backache since beginning of *July 1954*. At examination at end of month an abdominal mass to the left of the umbilicus was noted. Roentgen therapy: Field F (150 cm², Fig. 3), 30 July to 1 August, 250 r per day, total 750 r.

No evidence of the tumour on 1 *September 1954*. The patient still had severe backache, however, as well as difficulties in walking and urinary retention. Roentgen examination the same day revealed an 8 by 8 cm mediastinal tumour which was displacing the oesophagus, a left pleural effusion, and partial destruction of D 11. Roentgen therapy: Field A (400 cm²,

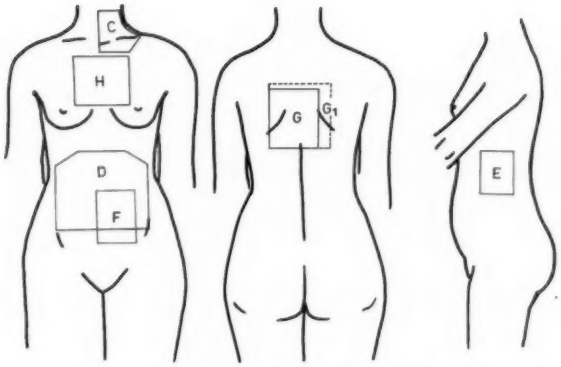

Fig. 3. Case 2. Anterior, posterior, and lateral areas of roentgen irradiation.

Fig. 2), 4 and 6 September, 150 r per day, total 300 r, field G (200 cm², Fig. 3), 7 to 13 September, 250 r per day, total 1 500 r, field A (400 cm², Fig. 2), 15 to 20 September, 150 r per day, total 1 050 r and field H (200 cm², Fig. 3), 21 to 30 September, 150 r per day, total 1 200 r. Roentgen examination on 27 September showed considerable regress of the mediastinal tumour, which had completely disappeared by 7 December 1954. The compression of D 11 remained unchanged up to the last examination on 19 June 1957.

Gradual general improvement. Started walking by the end of *November 1954*. Roentgen therapy: Field G (250 cm², Fig. 3), 4 to 11 March, 200 r per day, total 1 400 r.

No signs of recurrence until 2 November 1955, when a metastasis in the left supraclavicular region was noted (cf. 17 April 1953). Roentgen therapy: field C (100 cm², Fig. 3), 2 to 8 November, 400 r per day, total 2 000 r.

At controls afterwards no signs of recurrence was noted. The general condition of the patient improved steadily, and she walked without difficulty. Completely well on 21 October 1960, five years after treatment of the last metastasis.

Results of treatment

Fifty-six of the 60 patients in the material were referred to Radiumhemmet 5 or more years ago. Of these, 13 were admitted 25 or more years ago. The observation time for the patients is seen in Table 6.

Among the patients treated 5 or more years ago 14 have died from the disease and two have died from other causes (traffic accident and chronic glomerulonephritis 8 and 24 years respectively after diagnosis of the disease). Three patients were lost track of after 7 to 10 years of observation. These follow-up results imply that the five-year survival rate is 75 per cent. Among the four patients admitted since 1956 three are well. In one a recurrence has been diagnosed.

Recurrence was observed rather frequently; in the group surviving 5 years or more this was noted in 15 cases or 36 per cent.

Table 6

Time in years after admission for treatment (60 cases)

Years:	≥ 25	20—24	15—19	10—14	5—9	3—4	1—2
Number of patients	13	26	33	44	56	58	60
Living	5	12	17	28	37	39	41
Died from the tumour ..	5	9	11	11	14	14	14
Died from other causes .	1	2	2	2	2	2	2

The extent of the disease at the time of operation bears a close correlation to the prognosis. A survey is given in Table 7 of the influence of various factors suggesting progression of the disease beyond the ovary at the time of surgical exploration. The complications considered here are ascites, adhesions or rupture of the tumour, and metastases or bilateral involvement of the ovaries. For the sake of comparison the patients with the tumour localized to one ovary and without any of these signs of extension have also been included in the table. It will be seen that the presence of any of these complicating conditions, with the possible exception of ascites, carries a very serious prognosis.

The rapidity of the progression of the disease in cases in which radical surgical treatment was impossible, or the length of the interval before a recurrence, seem to yield considerable prognostic information. This is apparent from Table 8 where the time factor as regards progression or recurrence of the disease has been related to the outcome. Among the 14 patients who died from the tumour, 10 had an almost immediate flaring up or progression of the morbid process after surgical intervention. On the other hand, half of the surviving patients had their recurrence more than a year after the operation.

An analysis of the post-operative course for these patients may illustrate the effect of radiotherapy as well as the influence of the dose of radiation on the cure rate. Table 9 is a summary of the 56 cases treated 5 or more years ago. Among these patients 12 were suffering from definite extension of the disease

Table 7

Relation between extension of the disease at the time of operation and prognosis (only cases treated with combined surgery and radiotherapy 5 or more years ago have been included in this table)

Extension of the disease at operation	Number of patients	Five-year survival rate (%)	Recurrence rate (% of living)
Tumour encapsulated and movable .	22	95	14
Ascites	5	100	40
Tumour adhesions	8	75	50
Rupture of tumour before or at operation	5	60	0
Metastases (including bilateral ovarian involvement)	12	33	25

Table 8

Relation between rapidity of progression or recurrence of the disease and prognosis (only cases treated 5 or more years ago have been included in this table)

Time interval between operation and progression or recurrence of the disease	Number of patients	Five-year survival rate (%)
≤ 2 months	11	9
3 to 6 months	3	33
7 to 12 months	6	66
> 1 year	6	100

beyond the ovary and surgical removal of the tumour was incomplete. A further 4 patients were admitted for radiotherapeutic treatment because of recurrence after surgery. In 9 of these 16 patients the outcome was fatal. In 7 of the patients, however, the cure may be ascribed to the radiotherapy. Among the remaining 40 patients there were 13 recurrences; 8 of these have survived for five years or more after the beginning of treatment. These results thus show that the present series includes 29 patients who at the beginning of radiotherapeutic treatment or later were suffering from clinical manifestations of the disease. The five-year survival rate in this group is 52 per cent. These results clearly indicate the value of radiotherapy in the treatment of these tumours.

From Table 10, however, it is obvious that progression or recurrence of the disease was often noticed in areas previously irradiated. The material has been grouped in the table according to the dose of radiation given in the first course of treatment as well as to the incidence of recurrence and its topographical relation to the area of radiation treatment. It is seen that low doses of radiation (less than a total dose of 1 500 skin r per area) have a lesser therapeutic effect than higher doses. The groups are admittedly small, but the trend seems uniform throughout. It is evident that in the majority of cases there was recurrence in areas previously irradiated with low-to-average doses. Increased doses of

Table 9

Incidence of progression or recurrence of the dysgerminoma after the first series of radiotherapy (only cases treated 5 or more years ago have been included in this table)

Extension of the disease at operation	Number of patients	Progression or recurrence	Five-year survival rate (%)
A. Post-operative treatment			
Tumour encapsulated and movable	22	4	95
Ascites, adhesions, or rupture	18	9	78
Metastases (including bilateral ovarian involvement)	12	9	33
B. Not referred until appearance of recurrence after surgery			
Tumour encapsulated and movable	4	2	75

Table 10

Relation between dose of radiation in the first series of treatment and prognosis (only cases treated 5 or more years ago have been included in this table)

Total dose of radiation	Extent of condition at operation	Number of patients	Metastases in radiated area	Metastases in non-radiated area only	Five-year survival rate (%)
A. Post-operative treatment					
< 1 500 r per area	Tumour encapsulated and movable	19	2	1	95
	Ascites, adhesions, or rupture	10	4	2	60
	Metastases (including bilateral ovarian involvement)	8	7	0	12
> 1 500 r per area	Tumour encapsulated and movable	3	1	0	100
	Ascites, adhesions, or rupture	8	2	1	100
	Metastases (including bilateral ovarian involvement)	4	2	0	75
B. Not referred until appearance of recurrence after surgery					
< 1 500 r per area	Tumour encapsulated and movable	2	1	0	100
> 1 500 r per area	Tumour encapsulated and movable	2	1	0	50

radiation cured more than 50 per cent of these patients.

Death occurred comparatively early in the fatal cases. Nine patients died before the expiration of the first year; the remaining 5 patients died within 5 years.

Eighteen pregnancies occurred in 10 patients after treatment. There were 15 normal babies, one interruption of pregnancy on medical indications, one abortion, and one malformed child.

Discussion

Incidence of dysgerminoma. Dysgerminoma is a rare tumour. In KLAFTEN's material it represented 3.1 per cent of his total ovarian tumours. The figure given by NOVAK & GRAY is in the same range. SJÖVALL, in a considerably larger material of 678 ovarian tumours, reported an incidence of only 0.7 per cent, whereas SANTESSON (1947), in a series of 707 ovarian neoplasms, found 27 pure dysgerminomas, thus constituting 3.7 per cent of the total. As pointed out by this writer, however, the material was selected and shows an over-representation of tumour cases that are benefited by radiotherapeutic treatment.

Its predominant occurrence in young women is clearly borne out by this study. This trend is in agreement with most other reports in the literature

(6, 19, 24, 25, 28, 33). The peak of incidence is in the third decade of life. The youngest patient in the series was 8 and the oldest 44 years old.

Genital development and function. The association between dysgerminoma and developmental and sex changes has been emphasized in earlier papers, particularly in those by the pioneer in this field (MEYER). The tumour has often been reported in hermaphrodites and pseudo-hermaphrodites, and in patients with other genital malformations. In the course of time, however, the opinion has gained ground that the majority of dysgerminomas occur in apparently normal women. Thus in a series of 17 patients NOVAK & GRAY found only 3 cases with evidence of malformation of the external or internal genital organs. SJÖVALL comes to the same general conclusion as does SANTESSON. In the present series 5 patients had more or less marked developmental anomalies in the genital region. The connection between dysgerminoma and genital malformations does not therefore seem to be as close as was originally presumed.

The signs of normal sexual function found in the majority of the patients of the present series is, on the contrary, impressive. The age at inception of menstruation ranged from 12 to 17 years. Menstruation was normal in most cases and irregularities were only rarely encountered. Thirteen patients had been pregnant before the removal of the tumour. The observation that dysgerminomas are often found in normally fertile women has been repeatedly made (28, 33), although NOVAK & GRAY stated that a large proportion of these patients are sterile both before and after conservative operation. The connection between pregnancy and the diagnosis of the tumour in this series is noteworthy. It was apparent in 7 patients, and in an additional patient a recurrence was observed 6 weeks after the interruption of pregnancy. Such observations have often been made before (3, 4, 8, 13, 37). Whether the state of pregnancy bears any relationship to the development of the tumour, or whether the diagnosis of the tumour in connection with pregnancy is due to the more frequent examinations usually performed in these patients is a matter of conjecture.

The extent of the surgical procedure. Surgery has its given and indisputable place in the treatment of dysgerminoma. There has, however, been discussion on the problem of the radicality of the surgical procedure, i.e. whether bilateral salpingo-oophorectomy should be consistently carried out. When both ovaries are involved in the pathologic process extensive surgery is obviously necessary. FÖDERL estimated that the tumour appears bilaterally in approximately a third of all cases. PEDOWITZ, FELMUS & GRAYZEL mentioned a somewhat lower figure, in the neighbourhood of 17 per cent. In the present series bilateral involvement occurred in 7 patients or in about 11 per cent. It would therefore seem that the contralateral ovary is apparently normal in 70 to 90 per cent of patients at the time of operation.

As these patients are usually in their second or third decade and therefore in the prime of their reproductive life, there has in some quarters been reluctance to recommend radical surgery in cases with an apparently intact contralateral ovary (23, 26, 28, 33). This attitude has, however, lately been strongly criticized by Pedowitz et coll. In their material of 102 cases, in part collected from the literature, they found a very high incidence of post-operative involvement of the contralateral ovary. This occurred in 36.2 per cent of cases in a series of 47 cases of encapsulated dysgerminomas which were adequately followed. In an analysis of the end-results of attempts to preserve fertility by conservative surgery in 64 cases of dysgerminoma they found that the reproductive function had been retained only in 18 cases. In all other cases ovarian function had to be destroyed postoperatively, because of recurrence, or metastases necessitating roentgen therapy, or a further surgical operation. They summarize their experience by stating that 'conservative surgery, performed to preserve fertility is almost always ultimately futile and, in view of the high degree of malignancy of dysgerminoma and the frequency of bilateral involvement, is not warranted'. Pedowitz et coll. therefore advocated extensive surgery in every case, carried out as bilateral salpingo-oophorectomy and total hysterectomy. The rationale for this therapy is, according to these authors, the great risk of subsequent involvement of the contralateral and, at operation, apparently normal ovary. This great risk is not borne out by the present study. In patients who had been subjected to unilateral salpingo-oophorectomy and who had received post-operative roentgen treatment, dissemination to the remaining ovary occurred in 3 of them or 7.5 per cent.

Analysis of certain factors related to prognosis. The five-year survival rate in the present series is 75 per cent. As the series consists of the augmented material of Santesson (1947) the percentage is, as might be expected, in good agreement with his figure as well as with those presented by Mathieu & Plauchu of 66.7 and 63.8 per cent respectively. These survival rates are in sharp contrast to those reported by Mueller, Topkins & Lapp of 27.3 per cent, and by Pedowitz et coll. of 27.1 per cent. It seems of interest to analyze and establish the factors that may possibly have a bearing on this considerable divergence in therapeutic results.

A critical examination of differences between the series of patients treated at Radiumhemmet, and at most other institutions, indicates that the disparity in the results may be mainly due to three factors: selection of the patients included in the series, the treatment adopted, and the routine of follow-up examinations.

In conformity with the principles applied by Santesson, only pure dysgerminomas have been included in the present study. It is evident that this distinction has not been made earlier. Apparently most series of dysgerminomas reported have contained both pure dysgerminomas and dysgerminomas with

various structural combinations of other germ-cell tumours. The considerable difference in the prognosis for pure dysgerminomas and the other less differentiated germ-cell tumours has been clearly demonstrated by SAN ESSON (1947) and SANTESSON and MARRUBINI (1957). In a review of 17 cases of these latter tumours it was shown (29) that in all patients followed up for a sufficient length of time, i.e. in 16 patients, the process ran a fatal course within 2.5 to 9 months. Of these 17 tumours 5 showed a partly dysgerminomatous structure. When dealing with different types of tumours belonging to the same group and showing such definite differences in their response to therapy — from no noticeable effect (less differentiated germ-cell tumours) to a considerable response (pure dysgerminoma) — it seems of decisive importance rigidly to isolate the various groups for study. Only then can the malignant potential of the pure dysgerminoma be ascertained and a proper evaluation of the gains and risks involved in radical or conservative therapy be possible.

The second factor of importance in the attainment of the results at Radiumhemmet seems to be the consistent application of post-operative radiotherapy. The marked radiosensitivity of the dysgerminoma has been frequently reported (12, 25, 28, 33). Our Case 2 with the successful treatment of the repeatedly appearing metastases at different sites, is an excellent exemple of the susceptibility of the tumour to radiotherapy. This is further borne out by the above analysis of the response of recurrences to roentgen treatment in sufficient doses. Radiotherapy, however, is not generally adopted in the treatment of dysgerminoma. Thus, for instance, in the series of PEDOWITZ et coll. only 42 per cent of the patients received post-operative roentgen therapy, and no such therapy was given to over 20 per cent of those patients who had recurrence of the disease. Of significance seems to be irradiation not only to the region of the removed tumour but also to the para-aortic and epigastric lymph nodes. This view has been stressed earlier (28, 33).

The third factor of importance seems to be the routine of regular follow-up examinations at short intervals after the initial treatment. As recurrence usually occurs during the first year after operation (Table 8), and as in spite of a considerable recurrence rate a high five-year survival rate has been attained in this series, it appears that the immediate institution of radiotherapy to any metastases is essential.

The distribution among a series of patients with a more or less advanced state of the disease will considerably influence the therapeutic results. Early diagnosis is a decisive factor. As has been shown here, the five-year survival rate in patients with the dysgerminoma confined to one ovary and with an intact capsule is 95 per cent, whereas indications of progression of the morbid process beyond the ovary imply a considerably more grave prognosis (Table 7). These results are in line with those of several earlier reports (19, 25, 28).

The age distribution also seems to influence the over-all results. As shown in Table 1, the five-year survival rate is lower in the age groups 10 to 19 years and 40 to 49 years as compared with the age group of 20 and 39 years. The former

Table 11

Treatment and prognosis (only cases treated 5 or more years ago have been included in this table)

Treatment*	Number of cases	Extent of condition: Adhesions	Extent of condition: Rupture	Extent of condition: Metastases**	Five-year survival rate (%)	Recurrence rate (% of living)
Conservative surgery + conservative radiotherapy	17	4	1	2	94	25
Conservative surgery + extensive radiotherapy	23	6	3	7	65	20
Extensive surgery + extensive radiotherapy	12	3	4	3	67	13

* Conservative surgery: one ovary completely or partially left; extensive surgery: both ovaries removed; conservative radiotherapy: no direct irradiation towards the remaining ovary; extensive radiotherapy: irradiation to the total pelvis (in addition to other areas, see text).
** Bilateral ovarian involvement included.

age groups also have a considerably higher rate of recurrence. The increased mortality rate in patients before the menarche and after 40 years of age has been noticed earlier (15, 25, 27).

The extent of combined surgery and radiotherapy. On the basis of the results and discussion presented above it seems reasonable to conclude that the combination of surgery and post-operative radiotherapy is the method of choice in the treatment of dysgerminoma. A point of interest is the evaluation of a possible increase in morbidity and mortality following conservative surgery and radiotherapy as compared with more extensive procedures. The problem is whether methods aiming at the preservation of ovarian function are justified or expose these patients to greater risk.

Among the 56 patients treated 5 or more years ago surgery was combined with radiotherapy in 52 instances. In 40 patients conservative surgery, performed to preserve fertility, was carried out. In 23 of these patients the extent of the disease was considered to require a full course of radiotherapy with irradiation to the whole pelvis (as well as epigastric and corresponding dorsal areas). In 17 patients no direct irradiation was given to the remaining ovary. Thirteen patients were treated with bilateral oophorectomy and a full course of radiotherapy. The hazards and benefits of the different combinations of procedures have been estimated in terms of five-year survival rate and frequency of recurrence (Table 11). The frequency of the incidence of rupture of the tumour, metastases, and evidence of infiltrative growth at the time of operation have also been included in the table. It is obvious that the different groups are not the same as regards spread of the morbid process at the beginning of treatment and that they cannot therefore be compared. It may, however, be concluded that satisfactory results have been achieved in the group treated with conservative surgery and radiotherapy.

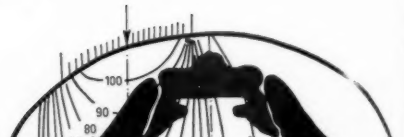

Fig. 4. Dose distribution in a pelvis phantom using 200 kV roentgen rays. Level of surface LV — SI. Transverse diameter 31 cm, sagittal diameter 20 cm. Size of irradiated areas 10 by 15 cm, 20 mA, FSD 40 cm, filter 0.5 mm Cu + 1.0 mm Al. Dotted line, 2.6 cm from midline, indicates medial limit of left ovary.

Genetic effects of conservative radiotherapy. Conservative, post-operative radiotherapy has been advocated earlier (5, 22, 23), but only single cases have been presented. The series from Radiumhemmet contains the largest number of patients that have as far as possible been consistently treated in this way. The possible harmful effects caused by this therapy constitute a special problem. Although no roentgen treatment is given directly to the remaining ovary, a considerable dose will still reach it by way of secondary irradiation. This is clearly recognized at Radiumhemmet, as is also the risk of damage to the hereditary material of the gonad, with transmission of induced mutations to the progeny as a consequence. Criticism has been levelled at conservative radiotherapy with this in mind (25). The genetic effects, however, have been referred to in general terms, and no attempt to evaluate, and if possible quantitatively estimate, the genetic harm that may be done to these patients has yet been made. It would seem that the special situation of these often very young patients requires a more detailed consideration of the genetic problems involved in conservative radiotherapy.

The experimental basis for a discussion on the mutagenic effects of radiation in humans is very scanty. Studies of congenital abnormalities in children of American radiologists (1, 14), as well as the extensive genetic study of the effects of the atomic bomb (21, 31) do not present conclusive material for providing direct evidence of the relation between the dose of radiation and the incidence of hereditary traumata in man. It has therefore been considered necessary to make an indirect estimate of the minimum radiation dose above which must lie the doubling dose, i.e. the radiation dose doubling the spontaneous mutation rate (16, 20, 39). The British Medical Research Council (16) considers this dose to be somewhere between 15 and 150 r, whereas the American National Research Council (20) and the United Nations Report (39) give the somewhat more restrictive figures 10 and 100 r.

A typical program of conservative treatment is to irradiate 6 areas (cf.

Fig. 1). As the ovaries are rarely found above a horizontal plane through McBurney's point their distance from the epigastric and corresponding dorsal areas is only exceptionally below 10 to 11 cm. A negligible dose will therefore reach the ovaries from irradiation of these areas as compared with the dose obtained from treatment of the contralateral pelvic and corresponding dorsal areas. This latter dose has been calculated on the basis of measurements in a tissue-equivalent (2) pelvis phantom. The isodose distribution is represented in Fig. 1. To avoid a possible underestimate of the effect of secondary irradiation, the ovary is considered to lie 2.6 cm from a midpoint of the uterus, which is the smallest distance reported (9, 11, 36). Under these premises approximately 10 per cent of the radiation dose to the pelvic and corresponding dorsal areas will reach the contralateral ovary, or in absolute figures approximately 100 r. The same magnitude of dose is arrived at when the calculations are based on the experimental work of KOTTMEIER on the in vivo dose distribution on irradiation of one side.

As mentioned above, the rather restrictively calculated figure of the American National Research Council (20) and the United Nations Report (39) for the doubling dose is between 10 and 100 r. Considering the fairly well established linear relationship between the frequency of induced mutations and radiation dose (35, 40), it is reasonable to estimate the dose of radiation reaching the remaining ovary under the conditions of conservative radiotherapy as somewhere between 1 and 10 times the doubling dose.

In order to illustrate possible hereditary effects of this radiation dose, it may be assumed that the highest figure calculated above, i.e. 10 times the doubling dose, is a fair estimate. The reliability of the information upon which the calculations of the increased risk of producing adversely affected descendants have to be based is, of course, open to criticism; the doubling dose is a hypothetical derivation, and the radiosensitivity of the individual genes in the different groups chosen below is probably highly variable. It is, however, possible to obtain a general idea of the effects of increased mutation rates upon the incidence of disease in descendants of radiation-exposed patients. Furthermore, it is evident that the estimations are here based on premises which probably lead to an overestimation of the risk imposed on these patients.

The incidence of low grade mental deficiency in the population is approximately 5 per cent (16). The increased proportional risk for a parent exposed to a dose of radiation doubling the causal genes of this defect is 1.5 per cent (16) and in our case consequently 15 per cent. The risk of her having a child with low grade mental deficiency is thus increased to approximately 5.9 per cent. The risk of bearing psychotic progeny may, if the mutation rate in one parent has been doubled, be increased by a factor of 0.6 per cent (16). The incidence of manic-depressive reactions and schizophrenia has been estimated as 0.3 per cent (39), and the risk for descendants of our hypothetical patient is accordingly increased to 0.56 per cent. The phenotype frequency at birth

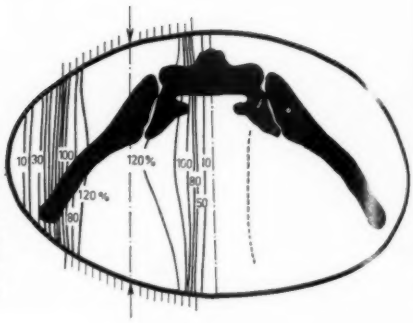

Fig. 5. Dose distribution in a pelvis phantom using cobalt 60 gamma radiation given with kilocurie cobalt unit loaded with 4 000 C. Level of surface LV — SI. Transverse diameter 31 cm, sagittal diameter 20 cm. Size of irradiated areas 10 by 15 cm, SSD 80 cm, penumbra trimmer. Dotted line, 2.6 cm from midline, indicates medial limit of left ovary.

of certain sex-linked recessive traits such as microphtalmus and gargoylism is approximately 12.5×10^{-6} (16). The increase in the first generation if mutation rates are doubled in one parent may be estimated as 20 per cent (16). The likelihood of our patient producing babies with these sex-linked recessive traits might therefore increase to 37.5×10^{-6}. The incidence in the population of certain diseases such as amaurotic idiocy, cerebral diplegia, phenylketonuria and 'true' microcephaly, all probably caused by autosomal recessive genes, is estimated as 0.1 per cent (16). The increased proportional risk for a parent where the mutation rate has been doubled is approximately one half per cent (16), and in our case consequently 5 per cent. The risk of her bearing a child with any of these defects is therefore increased from approximately 0.10 to 0.11 per cent.

The additional risk for further generations of inheriting genetic morbidity or harbouring a disposition for it is almost impossible to estimate. It is realized that the additional risk is perpetuated through an unforeseeable number of generations. Furthermore, it is necessary to bear in mind that the radiation-induced mutation process is probably irreversible, and therefore different from spontaneous mutations, where back-mutations have been observed (34). On the other hand, it is apparent that, due to dilution and natural selection, the chance of inheriting a radiation-induced allele is decreased in each generation by at least the factor 1/2 provided the spontaneous mutation rate in the population remains constant.

This matter has been gone into in some detail as a contribution to the discussion of radical treatment with extinction of fertility as against conservative surgical and radiologic treatment in certain cases with preservation of fertility but with certain genetic risks. In the light of the above calculations of the risk involved in unilateral pelvic irradiation, one has to realize that some hereditary damage may be caused. The practical consequences are negligible to society however, and reasonably small to the individual.

A the combination of unilateral oophorectomy and conservative radiotherapy is fully justified in certain patients from a medical point of view, it appears that removal of the contralateral ovary in these cases is undertaken for the purpose of sterilization and solely for genetic reasons. It would therefore seem mandatory in these instances to discuss the benefits and hazards of either procedure with the patient and to pay due attention to her wishes. It should be emphasized that, from the wider point of view, this question of obligation towards future generations to sterilize the radiation-exposed patients of this category, is not a completely isolated problem. If this is to be made a requirement for the radiation treatment of these patients, one will definitely be forced to examine critically the permissibility of treating patients with, for example, severe hereditary metabolic and psychiatric diseases. The subsequent child expectancy will thereby be raised for large groups of the population with considerably increased risks of perpetuating these diseases. Patients with dysgerminoma are, in principle, in the same situation as these other patients, and their dilemma as therapy-conditioned, potential producers of disabled descendants should be considered in its larger context. It is believed that the result will be greater reluctance towards radical methods, when these are not required for medical reasons.

Conclusions

The present study has shown the value of post-operative radiotherapy in the treatment of dysgerminoma of the ovary. It has also clearly demonstrated that conservative surgery combined with conservative radiotherapy is fully justified in certain cases in which preservation of the ovarian function is desired. On the other hand, an analysis of the relation between the dose of radiation and the prognosis indicates that the small-to-moderate doses given in the majority of these cases, are sometimes inadequate. In most instances, there was recurrence in areas irradiated with small doses. Intensified radiotherapy cured more than half of these patients.

These results necessarily lead to the conclusion that more intense post-operative radiotherapy may be desirable. The employment of conventional roentgen therapy in larger doses is acceptable in cases in which radiation is given to the whole pelvis. But in patients for whom unilateral pelvic treatment is planned, this form of therapy will render the preservation of the normal function of a remaining ovary almost impossible. Owing to the scatter of the roentgen beam a two- to threefold increase in our small-to-moderate doses will give the remaining ovary a dose of radiation close to that causing sterilization, and in any case an unsatisfactorily large amount from the point of view of genetic consequences. The scattering effect may be considerably decreased by using supervoltage radiation, and its adaptation to the post-operative treatment of dysgerminoma is therefore to be recommended. Among the advantage of this type of radiation sharper definition of the beam edge should be

mentioned. These considerations are illustrated in Fig. 5, where it is shown that the amount of radiation reaching the remaining ovary with kilocurie cobalt therapy is only a fraction of that obtained with conventional roentgen therapy (Fig. 4). The same effect may, of course, also be achieved with, e.g. the linear accelerator.

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SUMMARY

Sixty cases of dysgerminoma of the ovary, treated since 1921 are reported. Special attention is paid to the problem of the malignant potential of the tumour and the extent of the therapeutic procedures required. The possibility of inducing damage to the hereditary material of a remaining ovary by conservative radiotherapy, i. e. when no direct irradiation falls upon this ovary, is discussed in some detail.

ZUSAMMENFASSUNG

Der Verfasser berichtet über 60 Fälle mit Ovarialdysgerminom, welche seit 1921 behandelt worden sind. Besondere Aufmerksamkeit wird dem Problem des malignen Potentials der Tumoren gewidmet sowie dem Ausmass der erforderlichen therapeutischen Massnahmen. Die Möglichkeit, dass ein übriggebliebenes Ovarium nach konservativer Radiotherapie, d. h. wenn keine direkte Bestrahlung des Ovariums vorkommt, der Erbmasse einen Schaden zuführen könne, wird eingehend besprochen.

RÉSUMÉ

L'auteur présente soixante cas de dysgerminome de l'ovaire, traités depuis 1921. Il a étudié particulièrement le problème du potentiel malin de cette tumeur et l'importance des moyens thérapeutiques qu'elle nécessite. Il examine de façon assez détaillée la possibilité de lésion du matériel héréditaire de l'ovaire restant par la radiothérapie, quand cet ovaire n'est pas exposé à l'irradiation directe.

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EVALUATION OF CYREN-B AS A LEUKOCYTE PROTECTING AGENT IN PATIENTS UNDERGOING RADIOTHERAPY OR CHEMOTHERAPY FOR MALIGNANT LYMPHOMA

by

JOHN H. WEBSTER, ELLEN M. LESSMANN and JOSEPH E. SOKAL

A limiting factor in the radiation therapy and chemotherapy of malignancy is the leukopenia resulting from such treatment, which sometimes necessitates the interruption of therapy before a desired dose has been given. In the past, innumerable compounds have been used in an attempt to treat this complication, and none has been found to be clinically useful. In a recent report, BELLESIA, LUSVARGHI, PASQUINELLI and DARDARI (1957) claimed to have largely solved this problem by the use of diethyldioxystilbenedipropionate. This agent was selected for clinical trial after basic studies had indicated that estrogens of this type might increase the resistance of leukocytes to several types of injury (PEDERZINI et coll. 1955, and STORTI and PEDERZINI 1955). The conclusions of the clinical study were that this drug possessed a marked ability to prevent or ameliorate leukopenia induced by radiotherapy or nitrogen mustard therapy. There was no apparent interference with the therapeutic effects of either form of treatment.

Because of the desirability of confirming such an effect, if possible, it was decided to test this drug in a well-controlled study, using a series of patients treated by techniques which would usually induce leukopenia.

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Table 1

Method of classification of patients into 'high-risk' and 'low-risk' groups with respect to bone marrow depression

I. Previous therapy during the past two years
   1. One course of nitrogen mustard and/or irradiation of peripheral nodes only ..... Score 0
   2. Two courses of nitrogen mustard or one course of irradiation to the midline trunk ..... Score 1
   3. More than two courses of nitrogen mustard or more than one course of irradiation to the midline trunk ..... Score 2

II. Bone marrow status
   1. Normal marrow ..... Score 0
   2. Possibly depressed granulocytic elements ..... Score 1
   3. Definite depression of granulocytic elements ..... Score 2

III. Incidence of leukopenia during previous therapy
   1. Nitrogen mustard or irradiation of the midline trunk
      a. No leukopenia ..... Score 0
      b. Leukocyte count between 3 000 and 5 000/mm³ ..... Score 1
      c. Leukocyte count below 3 000/mm³ ..... Score 2
   2. Irradiation of peripheral nodes only
      a. No leukopenia ..... Score 0
      b. Leukocyte count below 5 000/mm³ ..... Score 2

Total score = Score I + Score II + Score III

Classification

Unlikely to develop leukopenia ..... Total score 0—2
Very likely to develop leukopenia ..... Total score 3—6

Materials and methods. The effect of diethyldioxystilbenedipropionate (Cyren-B, Bayer) was assessed in 67 patients with malignant lymphoma treated either with nitrogen mustard, 0.4 mg/kg body weight divided into four daily doses, or with radiation directed to the mediastinal or retroperitoneal areas. Because many of these patients had had previous courses of irradiation or chemotherapy and may have had varying degrees of bone marrow depression, they were subclassified into two groups before treatment was started, i. e. those more, and those less likely to develop leukopenia. This subclassification was based on the selection method described in Table 1. Patients with pre-existing leukopenia were excluded from this study. Patients were allocated to treatment and control groups according to a table of random numbers. The distribution of patients among the various treatment and control groups is shown in Table 2.

Cyren-B, 2.5 mg/ml in sesame oil, was administered intramuscularly in individual doses of 2.5 mg according to the following schedules:

1. Those patients undergoing nitrogen mustard therapy received daily injections starting the day before the first dose of nitrogen mustard and ending

Table 2

Distribution of patients among various study groups

	Nitrogen mustard		Radiotherapy	
	Treatment group	Control group	Treatment group	Control group
High risk	5	8	9	10
Low risk	7	7	9	12
Total (67)	12	15	18	22

the day of the fourth dose, a total of 12.5 mg of the drug being given in five days.

2. Those patients undergoing radiation therapy received injections of the drug three times weekly when their course of radiotherapy extended over a period shorter than four weeks, or every third day when their course of radiotherapy extended over a period longer than four weeks. Therapy with the drug was instituted when the accumulated tumor dose had reached 750 rads.

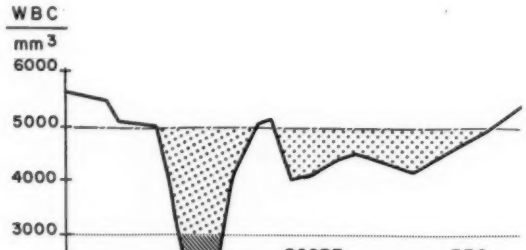
Hemoglobin and hematocrit determinations, leukocyte count, and platelet count were obtained at least twice before treatment. Upon the institution of radiotherapy or chemotherapy, leukocyte and platelet counts were obtained three times weekly, and hemoglobin and hematocrit determinations were made weekly. These observations were continued throughout the entire course of therapy and for a minimum of four weeks thereafter.

Evaluation of response. Leukopenia was evaluated at two levels, i. e., depression of the white blood cell count below 5 000, and below 3 000 per mm^3. This was done because of the possibility that a therapeutic effect might be manifested by prevention of severe leukopenia even though mild leukopenia occurred, and because patients with slight leukopenia might respond differently from those with a more profound leukocyte depression. White blood cell counts were graphed individually for each patient. The areas enclosed by

Table 3

Incidence of leukopenia and thrombocytopenia among the study groups

Patient category	No. of cases	WBC below 5 000/mm^3	WBC below 3 000/mm^3	Pl. below 150 000/mm^3	Pl. below 100 000/mm^3
Control, high risk, irradiated	10	10	6	6	2
Cyren-B, high risk, irradiated	9	7	4	6	4
Control, low risk, irradiated.....	12	10	3	6	2
Cyren-B, low risk, irradiated	9	5	4	4	1
Control, high risk, HN_2 treated.....	8	7	7	7	6
Cyren-B, high risk, HN_2 treated	5	4	3	3	2
Control low risk, HN_2 treated.....	7	6	5	5	3
Cyren-B, low risk, HN_2 treated	7	7	4	4	2
Total	67	56	36	41	22



Graph representing the white blood cell count of a roentgen irradiated patient and the determination of the leukopenia scores. Both the stippled and striped areas are included in the leukopenia score 'below 5 000', while only the striped area is included in the leukopenia score 'below 3 000'.

that part of the white blood cell curve below the line for 5 000 (or 3 000) cells per mm³ expressed both the severity and the duration of leukopenia. A representative graph of this type is given. A numerical 'leukopenia score' which was the product of the amount of depression of the leukocyte count below 5 000 (or 3 000) per mm³, multiplied by the number of days that such depression persisted, was determined for each patient. Thrombocytopenia was evaluated in a similar fashion, using 150 000 and 100 000 platelets per mm³ as the limiting lines. Cyren-B treated patients were then compared with the appropriate control groups, using both the Chi-square test and the rank-t test for analysis of differences in leukopenia and thrombocytopenia scores.

Results and Discussion

The incidence of leukopenia and thrombocytopenia encountered during or after the treatment of these 67 patients is shown in Table 3. From this table it is apparent that hematologic depression occurred frequently enough to provide a sample for evaluation, since the great majority of patients developed leukopenia and slightly over half, severe leukopenia. It also can be seen that there is no marked difference between the control and the Cyren-B treated groups. In the latter, three-fourths of the patients developed leukopenia and half, severe leukocyte depression.

For more precise evaluation, each group of Cyren-B treated patients was compared with its control group, using both the Chi-square test and the more

Table 4

Results of statistical analysis of leukopenia scores of Cyren-B treated and control patients

Classification	Mean leukopenia scores ± S. E. Controls	Cyren-B treated	x^2	t^2	P*
Nitrogen mustard					
High risk,					
WBC below 5 000	29.97 ± 8.42	13.37 ± 7.11	0.18	1.92	0.20>P>0.10
WBC below 3 000	7.29 ± 3.43	0.88 ± 0.45	0.07	1.23	0.30>P>0.20
Low risk,					
WBC below 5 000	39.80 ± 15.98	14.4 ± 4.57	0	1.17	0.30>P>0.20
WBC below 3 000	3.97 ± 1.82	2.86 ± 1.71	0	0.51	0.50>P>0.30
Roentgen irradiation					
High risk,					
WBC below 5 000	34.10 ± 9.43	32.99 ± 16.32	0.82	0.78	0.50>P>0.30
WBC below 3 000	3.94 ± 2.76	9.97 ± 7.79	0.05	0.26	0.70>P>0.50
Low risk,					
WBC below 5 000	14.85 ± 3.60	14.77 ± 6.35	0.82	0.26	0.70>P>0.50
WBC below 3 000	0.37 ± 0.35	0.99 ± 0.61	0.22	0.92	0.50>P>0.30

* The value of 'P' is associated with the value for t^2 since this was considered the most sensitive test.

sensitive rank-t test (Bross 1954, Wilcoxon 1945) for analysis of the differences in leukopenia and thrombocytopenia scores. Both tests failed to demonstrate a beneficial effect of the drug. The values derived from the application of these tests in the analysis of the leukopenia scores are presented in Table 4. The large standard errors seen in this table are due to the great variation in scores among the individuals comprising each group. The 'high risk' and the 'low risk' patients in each category were then combined in order to increase the size of the control and treatment groups and statistical analysis was repeated using the Chi-square test. Again, no significant advantage of treatment with Cyren-B was seen. While a slight advantage due to a real action of Cyren-B cannot be excluded for the nitrogen mustard group, these results indicate that this drug does not confer important protection against leukopenia or thrombocytopenia.

A by-product of this study was the opportunity afforded us to evaluate our criteria for assigning patients to 'high risk' and 'low risk' groups with respect to the hazards of inducing leukopenia and thrombocytopenia. Comparison of the course of control patients in the 'high risk' and 'low risk' groups revealed a difference of borderline significance ($0.10>P>0.05$) in roentgen irradiated patients with respect to leukopenia. The criteria listed in Table 1 proved to have no predictive value for nitrogen mustard treated patients, or for roentgen-irradiated patients insofar as thrombocytopenia was concerned. Since no significant difference was found between the control and the Cyren-B treated patients, these groups were combined and analysis of the differences between 'high risk' and 'low risk' patients was repeated. The significance of the dif-

ferences was not increased. It is apparent that our criteria for assessing the risks of leukopenia and thrombocytopenia need considerable improvement.

Acknowledgement

We wish to thank Dr. I. D. J. Bross for his help with the statistical evaluation. Diethyldioxystilbenedipropionate was kindly supplied by Farbenfabriken Bayer Aktiengesellschaft, Leverkusen, Germany and is available in that country as 'Cyren-B'.

SUMMARY

The alleged protective effect of diethyldioxystilbenedipropionate (Cyren-B) against radiation or nitrogen mustard induced leukopenia was investigated in 67 patients with malignant lymphoma. The patients were randomly allocated to treatment and control groups, and appropriate statistical techniques were used to determine whether this drug afforded any significant protection. No protective action of the drug against leukopenia or thrombocytopenia was seen. The authors were unable to predict the likelihood of developing thrombocytopenia or leukopenia in the individual patient about to undergo treatment.

ZUSAMMENFASSUNG

Der angenommene Schutzeffekt des Diethyldioxystilbenedipropionates (Cyren-B) gegen Leukopenie, welche durch ionisierende Strahlung oder Stickstoff-Senfgas hervorgerufen wird, ist bei 67 Patienten mit malignem Lymphom untersucht worden. Die Patienten wurden willkürlich einer Behandlungsgruppe bzw. einer Kontrollgruppe zugeteilt und geeignete statistische Methoden wurden benutzt um festzustellen, ob diese Droge irgendeinen signifikanten Schutz erbot. Keine schützende Eigenschaft der Droge gegenüber der Leukopenie oder Thrombocytopenie wurde beobachtet. Die Autoren waren nicht in der Lage, die Wahrscheinlichkeit eines Zustandekommens einer Thrombocytopenie oder Leukopenie bei den in Behandlung befindlichen individuellen Patienten vorauszusehen.

RÉSUMÉ

Le prétendu effet protecteur du dipropionate de diéthyldioxystilbène (Cyren-B) contre la leucopénie induite par les radiations ou les moutardes azotées a été étudié sur 67 malades atteints de lymphome malin. Les malades ont été répartis au hasard en groupes traités et groupes témoins et on a utilisé des techniques statistiques appropriées pour déterminer si ce produit donne une protection significative. On n'a constaté aucune action protectrice de ce produit contre la leucopénie ou la thrombocytopénie. Les auteurs n'ont pu prévoir l'apparition vraisemblable d'une thrombocytopénie ou d'une leucopénie chez les malades qui allaient être soumis à ce traitement.

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FRO THE RADIATION PHYSICS DEPARTMENT (DIRECTOR: ASSOC. PROF. KURT LIDÉN), UNIVERSITY OF LUND, SWEDEN.

CESIUM 137 BURDENS IN SWEDISH LAPLANDERS AND REINDEER

by

KURT LIDÉN

We measured the Cs 137 burdens in a group of Norwegians in October 1960 and found them to be several times higher than a normal control group drawn from the population of Lund, Sweden. In January 1961 a group of 15 subjects from Oslo and 6 from Bergen in Norway were measured in our whole body counter at Lund. The Oslo group showed an average Cs 137 burden of 21 nc and 180 pc/g K with a maximum value of 32 nc, 340 pc/g K, and the Bergen group an average of 60 nc, 480 pc/g K with a maximum of 106 nc, 810 pc/g K (BAARLI, LIDÉN, MADSHUS and MCCALL 1961). These values were partly a result of a goat's milk cheese diet; a Cs 137 content of goat's milk cheese as high as 41 nc/kg is reported from Norway.

We became interested in other groups in Scandinavia with unusual diets. We measured a sample of commercially available reindeer meat from an unidentified source in northern Sweden and found it to contain 28 nc/kg while beef from the Lund area showed less than 0.1 nc/kg. It was thus obvious that the people in northern Sweden on a reindeer meat diet, particularly the Laplanders, must have substantially higher Cs 137 burdens than other Swedes. We measured a Laplander, studying in Lund (code No. 107) in March 1961 and found that he showed 196 nc Cs 137. During the previous two years, he had spent most of his time in Lund and had therefore only occasionally eaten

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Table

Cs 137 and potassium content of three Laplanders and one subject from Lund

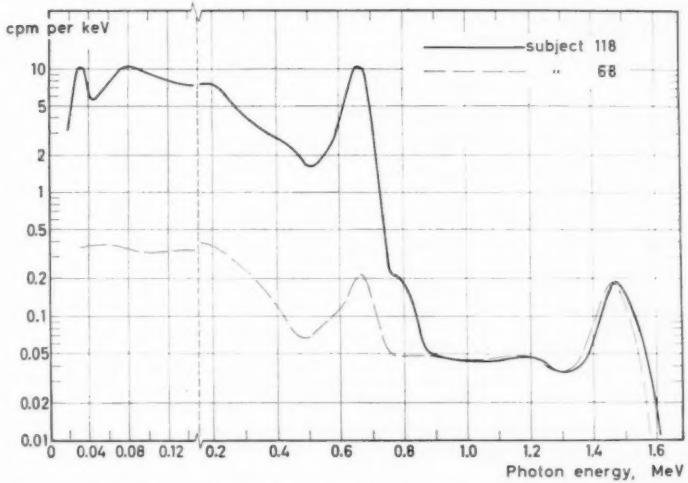
Code No.	Sex	Age years	Weight kg	Cs 137 nc	K g	Cs 137/K pc/g	Diet R = reindeer meat G = goat cheese
107	M	35	67	196	97	2 020	R occasionally G 20—50 g/day
118	M	46	52	361	107	3 360	R 200—400 g/day no G
119	F	34	56	242	90	2 690	R 200—300 g/day no G
68	M	23	57	5.9	98	60	no R, no G

reindeer meat; but he had had goat's milk cheese regularly, the Cs 137 content of which we found was high. His Cs 137 pattern was thus not to be one of pure reindeer meat. In order to prove the effect of a predominantly reindeer meat diet two reindeer-raising Laplanders from latitude 66.6° N were also measured (at the beginning of May 1961) in our iron room (code Nos 118 and 119). The result of the three Laplanders studied is given in the Table above. For comparison, data for a subject in the control group of Lund are also given. Cases 118 and 119 show a Cs 137 activity 45 and 30 times as high as the average of 8.0 nc of the local control group of Lund and 3.4 and 2.3 times as high as the highest value in the Norwegian group mentioned above.

The spectrum of case 118 is shown in the figure. Above 150 keV it was obtained with a 5″ diam. × 4″ thick NaI(Tl) crystal at 25 keV per channel with the subject in the Argonne chair geometry; below 150 keV a thin crystal assembly with two 110 mm diam. × 5 mm thick NaI(Tl) crystals in parallel was used (LIDÉN and MCCALL 1961). The Ba $K\alpha$ roentgen line at 32 keV is easily identified. This may be the first time that this line has been observed and identified in the spectrum of a normal human being. There is also a bump in the high energy slope of the 0.662 MeV peak, the origin of which is not obvious; a small body burden of (Zr + Nb) 95 may be a possible explanation. This bump is slightly more marked in the reindeer meat spectrum. The matter is being further studied.

Measurement of reindeer meat produced in the area where cases 118 and 119 are living gave a Cs 137 content of 24 nc/kg. The Cs 137 activity in adult reindeer is probably of this order of magnitude in most parts of Scandinavia.

If the daily intake of meat is known, the body absorption of Cs 137 from the gastro-intestinal tract may be calculated. Using a biologic half life for Cs of 74 days, obtained from an intravenously injected subject of the same age as case 118 and studied in Lund for 7 months, the excretion ought to be 0.94 % per day and thus, if equilibrium exists, the intake must be the same. If Cs 137 is taken in from reindeer meat only, 300 g a day corresponds to about 7 nc



Spectrum of a Swedish Laplander with a Cs 137 burden of 361 nanocurie (code No. 118) and a subject from Lund with a Cs 137 burden of 5.9 nc (code No. 68). Above 0.15 MeV the spectrum is measured with a 5″ diam. × 4″ thick NaI(Tl) crystal at 25 keV per channel; below 0.15 MeV two 110 mm diam. × 5 mm thick NaI(Tl) crystals in parallel have been used at 4 keV per channel. The measurements are made in Argonne chair geometry. Both subjects contain approximately the same amount of potassium, 107 g and 98 g, respectively.

Cs 137; the measured Cs content of 361 nc in case 118 then corresponds to an absorption of roughly 50 % of the Cs 137 introduced orally. This figure will be studied more carefully using the reindeer meat as a naturally labelled substance.

A Cs 137 content of the soil of 14—42 nc per m² is reported from Sweden at latitude 63° N (LÖW and EDVARSON 1960). Other parts of Sweden show 18—26 nc/m² with an average in both cases of 20 nc/m². The explanation of the high Cs level in reindeer is very likely to be found in their habit of grazing on lichens and herbs over large areas of ground; we have measured Cs 137 activities in lichens of 10 to 30 nc/kg. The reindeer food and its metabolism have to be studied in more detail before any relation between food activity and meat contamination can be established.

According to the recommendations of ICRP the maximum permissible body burden of Cs 137 is 3.0 μc for people outside controlled areas. Thus the Cs 137 activity in case 118 is about one tenth of this value, giving a yearly dose contribution of roughly 55 mrad, which is about three times the internal potassium dose and 50 % of the average human dose from natural sources of radiation in Sweden, 100 mrad per year.

The dose contribution from other internal sources is mainly due to (Sr + Y)

90. Attempts to determine this activity by external measurements wi our thin crystal method (LIDÉN and MCCALL 1961) are now being under ken. Our minimum detectable amount is at present 20 nc Y 90 if the effect the bodyweight on the background and on the Cs 137 spectrum is accu ately known. This requires further studies in the present case.

The number of Laplanders in Sweden is about 10 000; there are 20 00 in Norway, 3 000 in Finland, and 2 000 in Russia. According to HY ENIUS (1961) the reindeer-raising Laplanders in Sweden constitute a group of bout 2 600 people, who thus may have Cs 137 burdens similar to the values given above. No groups of subjects of comparable size and activity level have previously been reported. Extensive studies of the Swedish group will be undertaken by us and by other research institutes in Sweden. However, it is easy to see that groups of people with living habits similar to the Laplanders do exist in other countries. It is desirable that some of them should also be studied.

SUMMARY

Measurements in the whole body counter at Lund have shown the Cs 137 burden in Swedish Laplanders to be 20 to 40 times as high as in a control group of Lund. A diet of reindeer meat containing about 25 nc Cs 137 per kg is the main source of this unique Cs 137 level in human subjects.

ZUSAMMENFASSUNG

Messungen mit dem Ganzkörperzähler in Lund haben gezeigt, dass die Cs 137 Aktivität der schwedischen Lappen 20 bis 40 mal grösser ist als die Aktivität einer Kontrollgruppe in Lund. Tägliche Kost mit reichlichen Mengen von Renntierfleisch mit einer Aktivität von etwa 25 nc Cs 137/kg ist die Hauptursache für diesen einzigartigen Cs 137 Gehalt im Menschen.

RÉSUMÉ

Des mesures effectuées avec le compteur pour le corps entier de Lund ont montré que la charge en Cs 137 de Lapons suédois est de 20 à 40 fois supérieure à celle d'un groupe témoin de Lund. L'alimentation à la viande de renne contenant environ 25 nc de Cs 137 par kg est la principale source de ce taux unique en Cs 137 chez l'homme.

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